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INDEX

Pagina

Dose measurements on contact-therapy-tubes by W. J. Oosterkamp 491

Roentgenological studies of experimental pulmonary embolism without complicating infarction in dog by Sven Roland Kjellberg and Sten-Erik Olsson . . 507

Multiple myeloma by Lars Anda 515

On the diagnosis of atresia of the esophagus by Sigurd Eek, Leif Efskind and Aage Wolff 529

A rod-shaped gall stone by Rolf Köhler 535

The treatment of thyroid carcinoma with radioactive iodine by Sigvard Kaae and Olaf Petersen 539

Changes in the sacro-iliac joints in Morbus Bechterew and osteitis condensans by Folke Knutsson 557

Presentation of results of treatment of cancer by J. Heyman 571

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DOSE MEASUREMENTS ON CONTACT-THERAPY-TUBES[1]

by

W. J. Oosterkamp

I. Introduction

Dosage measurements on contact-therapy-tubes have been reported by various authors (1). These measurements show large discrepancies. For instance the extreme values of the relative depth dose at a depth of 10 mm and at a focus-skin distance of 20 mm are respectively 12 % and 32 % for the Philips type of apparatus (cf. Table II); a survey by CHAOUL, SCHATTER and WACHSMANN (2) with the Siemens type of apparatus shows extreme values of respectively 30 % and 70 % for the relative depth dose also at a depth of 10 mm but at a focus-skin distance of 50 mm.

It was therefore thought that a useful purpose would be served by making an analysis of the various causes of errors and carrying out a series of measurements in such a way as to eliminate these systematic errors as far as possible. Moreover the experimental data have been verified by theoretical calculations, which will be reported upon separately. Our investigations have been confined to the Philips type of apparatus.

There are several circumstances to which the large discrepancies can be attributed:

a. The dose varies very rapidly from point to point within a phantom, therefore the ionization chambers should have small dimensions.

b. The sensitivity of thimble chambers may be wavelength-dependent. This effect is more likely to interfere in contact-therapy measurements than under more conventional therapy conditions as in contact therapy the radiation is very soft and heterogeneous.

[1] Submitted for publication Jan. 9, 1950.

From Philips research laboratories, N. V. Philips' Gloeilampenfabrieken, Eindhoven-Netherlands.

c. The dose rates are very high, up to 8,000 r/min, and special precautions have to be taken to ensure saturation of the ionization current.

d. Secondary radiation may arise from the walls of the applicators and from the tube window. This radiation is much softer than the primary radiation and will therefore change the absorption characteristics and depth dose values of the beam.

e. Differences of inherent filter between different tubes caused by small differences in the thickness of the glass window have occurred, resulting in differences in dose rate and half-value layer of the emitted radiation.

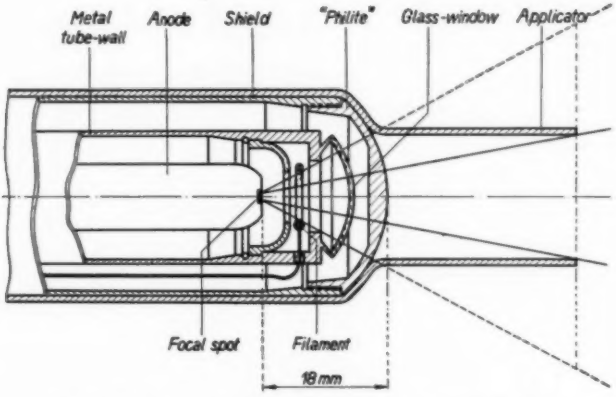

Fig. 1. Cross section of a contact-therapy tube.

For the sake of completeness a cross-section of the contact-therapy-tube is shown in fig. 1. The roentgen rays leave the tube through a glass window 0.3 mm thick and through a cap of »Philite» a plastic material with which the aircooled shield is closed. The tension is 50 kV constant potential; the tube current is 2 mA. The ripple of the high voltage is 3 kV. The tube current is stabilized, this facilitating accurate dose measurements. Standard filters of 1 and 2.5 mm Al can be used.

II. Measurement of the Absorption Characteristic in Aluminium

To characterize the radiation adequately a complete absorption curve in Al was determined. For these measurements a »Small Küstner Eichstandgerät», which instrument has a free-air ionization chamber, was used. This instrument was compared at regular intervals with a »Large Küstner Eichstandgerät», that had recently been calibrated at the National Physical Laboratory in England.

The measurements were taken at a focus distance of 150 mm in order

to reduce the dose rate. Moreover at this distance small errors in determining the focus distance have less effect than at a short focus distance. The inverse square law was used to convert the measured dose rate to a focus distance of 20 mm. For the unfiltered radiation a correction for air absorption of 3 % was made. We used a special calibrated entrance aperture of 2.0 mm Ø instead of the original aperture of the Küstner (11 mm Ø) in order to reduce the total ionization, which was necessary to

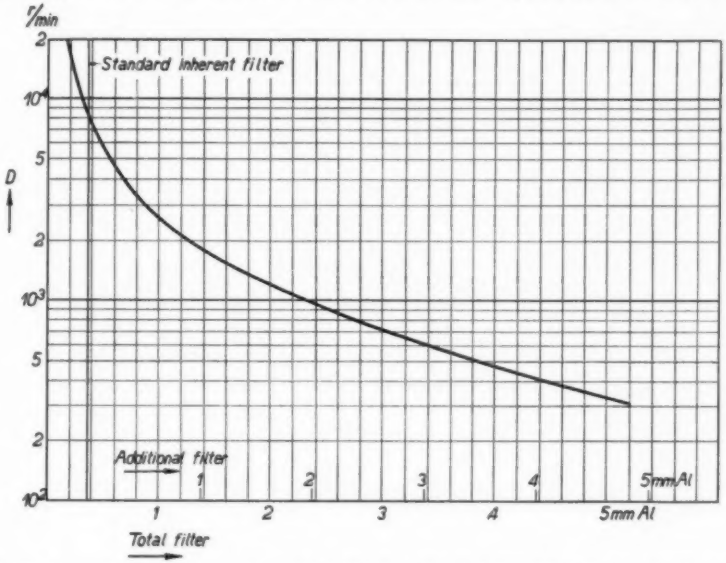

Fig. 2. Universal absorption characteristic in aluminium. 50 kV constant potential, 2 mA. Data converted to 20 mm focus distance. 2 abscissae are used, indicating the total filter and the filter to be added to standard tube.

obtain saturation at the highest dose rate of 140 r/min at 150 mm focus distance.

A number of tubes of which the inherent filter differed within a wide range were measured. The smallest inherent filter value was obtained with a special experimental tube having a window equivalent to 25 μ Al. This tube was used without Philite cap. When the dose rate of all tubes is plotted as a function of the total filter (inherent filter + added filter) it is found that all points lie on one curve (fig. 2) which we shall call the universal absorption characteristic (4).

In the past the output of different tubes varied between 7,000 and 10,000 r/min (in a few cases even considerably more) at 20 mm focus distance, due to slight differences in the thickness of the glass window.

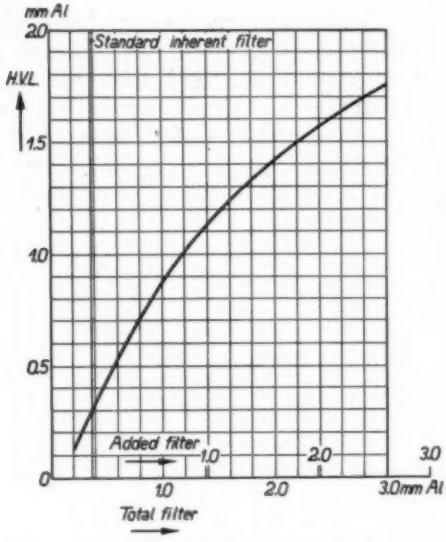

Fig. 3. The half-value layer in aluminium as a function of total or added filter. 50 kV constant potential.

The output is nowadays standardized at 7,500 r/min with a permissible deviation of $\pm$ 500 r/min. This is obtained by keeping the thickness of the glass window between closer tolerances; the residual difference is compensated by using »Philite» caps with different roentgen ray absorption. The equivalent inherent filter of these standard tubes is 0.36 mm Al.

The half-value layer of the radiation as a function of the total or added filter (fig. 3) can be deduced from the universal absorption characteristic. As the total filter approaches the zero value, the half-value layer also approaches zero. Table I gives the dose rate and half-value layer of the standard tube when using an additional filter of 0; 1 or 2.5 mm Al at a focus distance of 20 mm.

Table I

Output in r/min at 20 mm focus-skin distance, and half-value layer of standard tube. Inherent filter 0.36 mm Al.

Added filter (mm Al)	0	1.0	2.5
Dose rate (r/min)	8,000	1,800	750
H.V.L. (mm Al)	0.30	1.15	1.75

III. Field Distribution in Air

Fields with a cross section larger than half the focus-skin distance are not generally used in superficial therapy, because for larger fields the dose rate decreases too much towards the edges of the field, due to the larger distance to the focal spot compared with the center of the field. When the cross section of the field is equal to the focus-skin distance the difference is already 25 %. In contact-therapy a small focus-skin distance is used and it would be very disadvantageous if no larger fields than half the focus-skin distance could be used. By using graduated, so-

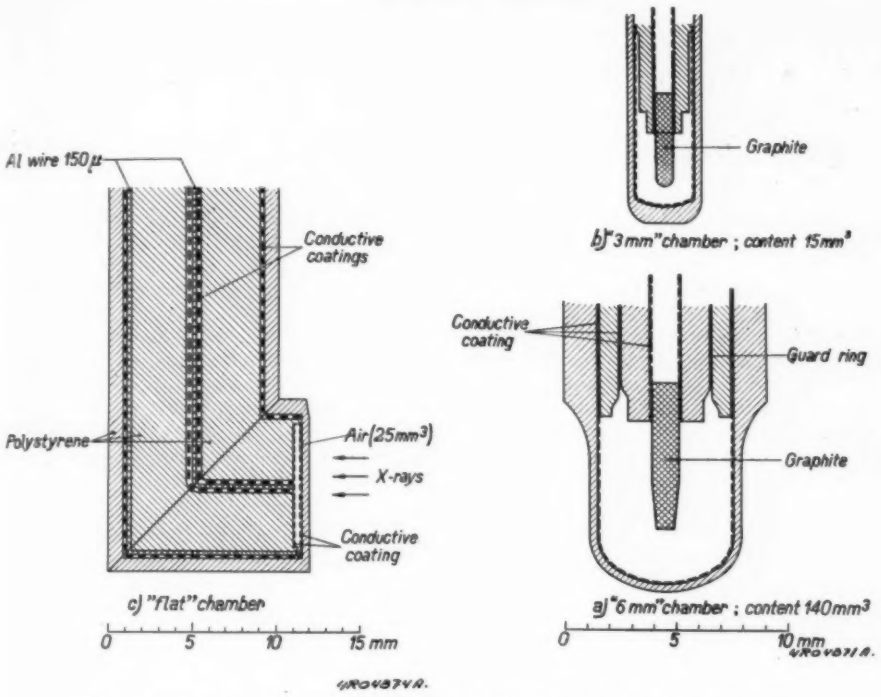

Fig. 4. »6 mm», »3 mm» and »flat» ionization chambers of polystyrene.

called compensation filters, which reduce the radiation in the centre of the beam more than at the edges, the size of the useful field can be considerably expanded. These compensation filters, with which all new tubes are provided and which can also be applied to tubes already in use, are made of Philite, a plastic material. The thickness is 2.5 mm in the centre decreasing towards the edges to 1 mm.

The field distribution with and without compensation filter has been investigated. The first measurements were taken with a small thimble chamber of 6 mm cross section (fig. 4 a), repeated later on with a 3 mm chamber (fig. 4 b). The voltage drop caused by the ionization current across a resistor of 50 MΩ for the »6 mm» chamber and one of 2,000 MΩ for the »3 mm» chamber was measured with a dynamic electrometer (fig. 5), described by van HENGEL and OOSTERKAMP (5). This is a direct-reading instrument. The high sensitivity of the instrument — thanks to the amplification — makes it possible to use the relatively small calibrated measuring resistors already mentioned. Consequently no great

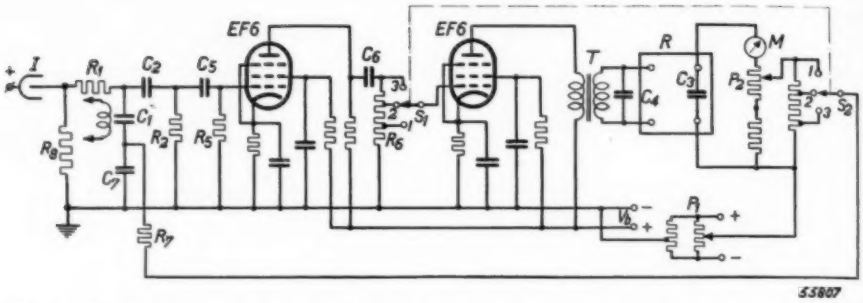

Fig. 5. Circuit diagram of dose meter with dynamic electrometer. The ionization current is causing a voltage drop across the resistance R_8; this direct voltage is converted into alternating voltage by a vibrating condensor C_1, then amplified by conventional radio valves and rectified. The voltage across R_7 can be read on the meter M. Negative feedback is applied to ensure high stability. The instrument has three ranges (switch S_1; S_2) of 100, 300 or 1,000 mV full scale deflection respectively.

demands need be made upon the insulation of the input terminal ($\geqslant 2 \cdot 10^{11}\ \Omega$), though actually it is to the order of $10^{14} - 10^{15}\ \Omega$.

Owing to the small size of the ionization chambers and thus small distance between the central collecting electrode and the wall of the thimble, the chambers are very well suitable for measuring high dose rates. Saturation was obtained at 200 V with the 6 mm chamber and already at 30 V with the 3 mm chamber, at the highest dose rate, 8,000 r/min, when the ionization chamber is in contact with the tube. The chambers were made of polystyrene, provided internally with an air-equivalent conductive coating consisting of a mixture of 92 % graphite, 6 % silicon and 2 % Zapon-lacquer dissolved in ethyl alcohol. Polystyrene when irradiated with roentgen rays becomes slightly conductive (6), which conductance, according to the experience under the conditions of these experiments, has ohmic properties, the leakage of these chambers under irradiation being of the order of 10^{12} Ohms. The voltage difference between the collectors should therefore be kept as low as possible.

The measurements of the field distribution were carried out by moving the ionization chamber along a track perpendicular to the axis of the tube. The distance between the successive positions of the ionization chamber was 1.5 mm. No limiting aperture in the beam was used. To get more accurate results the measurements were not taken at the shortest focus distance but at 40 mm. Subsequent measurements at 20 mm and at 200 mm distance taken with two tubes showed that the field distribution curves have the same shape, the size of the field being proportional

to the focus distance, as might be expected. The results are shown in fig. 6. With a compensation cap the dose rate is practically constant over a width of 30 mm and then slowly decreases; at a width of 40 mm the dose rate is still 85 % of the value in the center, when unfiltered radiation is applied. We believe that »cross section field equal to focus distance» should be the criterion for the maximum size of field to be used.

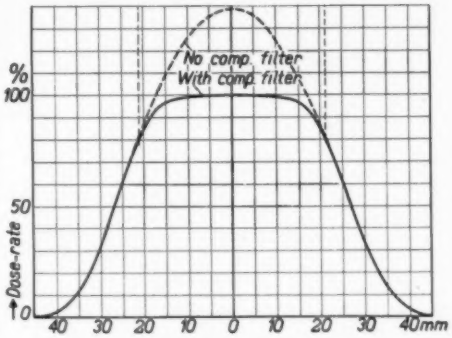

Fig. 6. Field distribution curves with and without compensation filter.

When filters of 1 or 2.5 mm Al are used the radiation is much harder and the effect of the »Philite» compensation cap is insufficient. In such a case the filters themselves can be given a compensating character by decreasing the thickness slightly towards the edges, from 1.0 and 2.5 mm respectively in the centre to 0.85 mm and 2.2 mm at the field limit, to obtain the same effect as in the case of unfiltered radiation.

IV. Depth-dose Measurements in a Water Phantom

We used water as a phantom material in a tank with walls of polystyrene 3 mm thick. A thin window of 0.2 mm polystyrene with a cross section of 50 mm was provided in the centre of one wall. The dimensions of the tank were 14 cm × 21 cm × 21 cm. The ionization chamber was fixed to a carriage that could be moved along tracks in two directions, respectively parallel and perpendicular to the axis of the tube. The position of the chamber could be read on two scales. As the effective atomic number of polystyrene is only slightly lower than that of water, the replacement of the water by the polystyrene of the structure of the ionization chamber has hardly any effect upon the radiation field. The radiation field is, however, considerably changed by the replacement of water by the air volume of the ionization chamber, unless the dimension of the ionization chamber in the direction of the primary beam is considerably smaller than the half-value layer of the radiation in water. In this respect the 3 mm chamber is still rather large for these measurements.

Measurements along the central ray.

In the central ray the isodose planes are practically flat and perpendicular to the central ray. Therefore an ionization chamber with

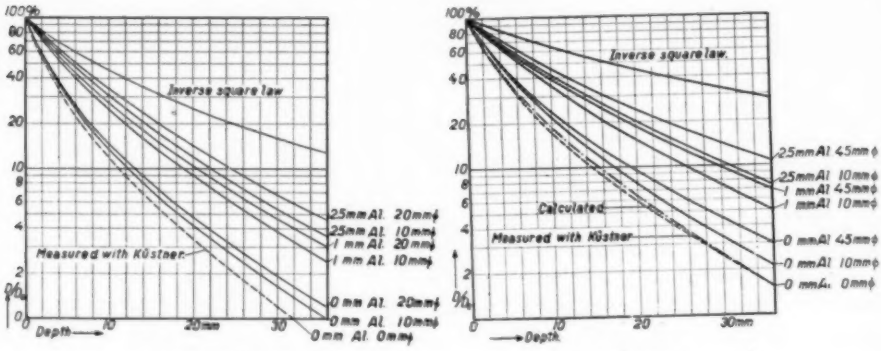

Fig. 7 a. Fig. 7 b.

Fig. 7. Relative depth-dose curves in a water phantom. 50 kV constant potential. The field size and the aluminium filter are indicated for the curves. Moreover a hypothetical dose-distribution, due to the inverse square law only, not taking into account absorption, is shown. a: 20 mm focus-skin distance. b: 40 mm focus-skin distance.

fairly large dimensions perpendicular to the central ray, to the order of 8 mm Ø, was used. This rendered it possible to make the dimension in the direction of the central ray (in which direction the dose rate varies rapidly) small, viz. 0.5 mm; the air volume was 25 mm³. This ionization chamber, also made of polystyrene is illustrated in fig. 4 c. The parallel planes are provided with the conductive coating, the one insulated from the other by a rim of uncoated polystyrene. Saturation for 8,000 r/min was obtained at only 10 V between the electrodes. At this potential difference the slight conductivity of polystyrene under irradiation with roentgen rays does not cause errors. The first flat chamber used was made with a fairly thick front wall of 0.7 mm thickness in order to ensure a constant volume. A thin wall may be easily distorted, especially when the chamber is used in a water phantom. Even small distortions can cause considerable changes in the size of the air volume, due to the small depth of the chamber. Nothwithstanding the rather thick wall the chamber was practically wavelength-independent compared with a standard ionization chamber for radiation with a half-value layer of 0.1 mm Al or more. A second execution of the flat chamber was made with a thin front wall of 0.02 mm polystyrene. As might be expected, it was also wavelength-independent in the investigated range of half-value layers. Comparative measurements in air made with both chambers showed a close agreement. In order to investigate the adequacy of the flat chambers the validity of the inverse square law in air between contact (18 mm focus distance) and a focus distance of 100 mm was checked with good results.

Table II

Depth dose in % at a depth of 10 mm as measured by various authors. Field appr. 25—30 mm Ø.

			Focus-skin distance:		20 mm			40 mm		
			Added Filter:		—	1.0 Al	2.5 Al	—	1.0 Al	2.5 Al
Author	Year	Material	Ionization chamber							
			shape and depth	window						
Smereker	1937	paraffine	thimble	0.5 mm C	26.5	—	—	—	—	—
v. d. Plaats	1938	water	thimble	thick	22.5	34	40	37	52	56.5
Den Hoed	1938	paraf.	—	—	32	—	—	—	—	—
Henschke	1940	paraf. + MgO	flat, 1 mm	0.02 mm cell	11.5	34	40	26.5	43.5	49.5
Braestrup + Blatz	1940	masonite	thimble	—	23	36	40	—	—	—
Lamerton	1940	water	flat, 2.5 mm	0.04 mm cell	16	30.5	36	26	40	51
Hultberg	1943	wax	flat	0.02 mm polyst.	19	35	40.5	25	43	47
Quimby + Focht	1943	pressed wood	flat 0.6—1.65 mm	0.58 mm lucite	17.5	32	34.5	23	—	—
Oosterkamp	1950	water	flat 0.5 mm	0.5 or 0.02 mm polyst.	15	27.5	34	23	37.5	44
Inverse square law	—	air	—	—	45	45	45	64	64	64

Depth-dose curves for 20 and 40 mm focus distance, 0; 1 and 2.5 mm Al filter and different field sizes are shown in figs. 7 a and 7 b. It should be borne in mind that the 100 % value at the surface is not equal to the dose rate measured free in air; the back-scatter should be added to the dose rate free in air. A comparison of the results obtained with those of other authors is given in table II. It is noteworthy that especially the early measurements show large discrepancies. Gradually the causes of errors were better understood.

The inside of the applicators which were used for measurements at 40 mm focus distance was covered with an Al foil of 0.03 mm thickness, to eliminate any secondary radiation from the walls of the applicators. The tube was provided with a compensation cap as described in section III and had an output free in air of 7,600 r/min. The data in figs. 7 a and 7 b for an infinitely small field were obtained from absorption measurements on layers of water of different thickness in a parallel beam and using the »Küstner Eichstandgerät». Application of the inverse square law to this data made them fit figs. 7 a and 7 b.

Back-scatter

The water phantom is not very suitable for measuring the back scatter at the surface, as there will always be the window of the water tank and a thin layer of water in front of the ionization chamber. Therefore back-scatter measurements were taken separately using a solid phantom consisting of 5 % gelatine and 95 % water with a flat face. A semi-cylindrical hole, in which one half of the 3 mm chamber fitted closely, was made in the face. Back-scatter was measured by determining the dose rate with and without phantom, with the ionization chamber at the same place for both measurements. The amount of back-scatter for unfiltered radiation is 4 % for a field of 10 mm Ø and 8 % for full opening. It increases slightly when Al filters are used, but this increase is so small that the data mentioned can also be hold good for the filters of 1 and 2.5 mm Al as well.

Non-standardized tubes

In section II it has already been shown how the inherent filter, and therefore the output of the tubes, has now been standardized. Since, however, there are still a number of tubes in use with an inherent filter and an output deviating rather considerably from the standard value, depth-dose measurements have been carried out with a tube having an extremely low inherent filter (0.18 mm Al as against 0.36 mm Al for a standard tube); its output was as high as 18,000 r/min at 20 mm focus-skin distance. The results of these measurements show that the depth-dose data of this tube are rather different from those of the standard tubes when expressed in the output free in air for unfiltered radiation. When expressed in the output free in air with a filter of 1.0 mm Al there is however only a (generally unimportant) difference within the first few millimeters of the phantom, whereas for a larger depth the curves coincide practically with those of the standard tubes.

Isodose curves

Owing to its large width the flat chamber is not suitable for determining isodose curves. Therefore the isodose curves were measured with the 3 mm chamber. The depth of this chamber is too large for accurate absolute measurements. Suitable correction factors were applied, so that in the central ray the data obtained with the 3 mm chamber coincided with those of the flat chamber. A typical example is shown in fig. 8 for a focus-skin distance of 20 mm and an aperture of 10 mm without additional filter. The fact that the 3 mm chamber is still comparatively large is demonstrated by the projection of about 1 mm of the measured isodose curves beyond the shadow of the aperture.

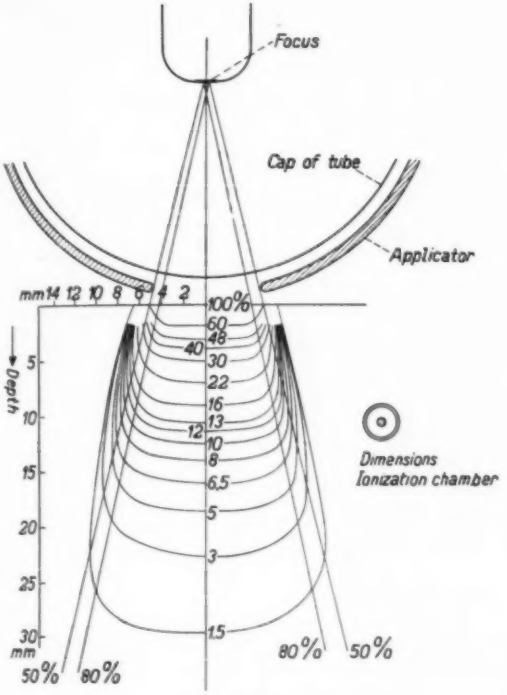

Fig. 8.

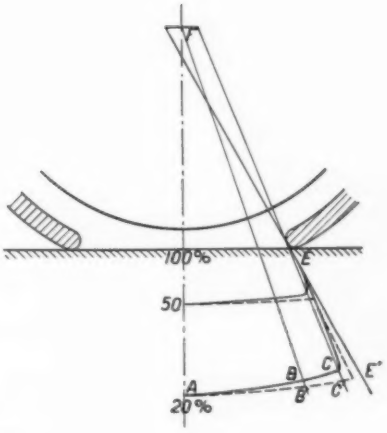

Fig. 9.

Fig. 8. The isodose curves for a focus-skin distance of 20 mm and an aperture of 10 mm; no additional filter; 50 kV constant potential. For comparison the relative dimensions of the ionization chamber are indicated.

Fig. 9. Construction of isodose curves. The value in the central ray is given by the depth dose curves (fig. 7). Proceeding from the central ray outwards, the shape of the isodose curve is such that a ray coming from the centre of the focal spot to a point B of the isodose curve traverses a slightly decreasing length of tissue (the difference is BB') to compensate for the decreasing contribution of scattered radiation to the total dose at a certain point. At the edges of the field from C to E there is a half-shadow effect due to the size (approximately 3 mm Ø) of the focal spot. The dose rate is approximately reduced to 40 % at the line FE passing from the center of the focal spot through the edges of the aperture. Outside FE the dose rate decreases rapidly.

Isodose curves for other apertures and focus-skin distances can be constructed as illustrated in fig. 9. For every point of the field the rays pass perpendicularly through the tube window and any Al filters that may be used. This, combined with the use of the graduated cap for compensating the effect of the inverse square law, has a favourable effect

on the shape of the isodose planes, which are practically parallel to the surface over a wide region beyond the central ray.

Secondary radiation from the applicators and from the tube window

The absorption of roentgen rays is accompanied by the emission of characteristic radiation by the absorber. When transmission targets are used the absorbing material is metal. MEREDITH (8) reported that the dose rate caused by the secondary radiation of the tube window in a tube with transmission target amounted to 25 % of the primary radiation. This secondary radiation originated mostly from the nickel backing of the target. The characteristic K radiation of nickel has a wavelength of 1.65 Å and is considerably softer than the primary radiation; therefore its presence greatly influences the depth-dose data. In tubes of the type discussed in this paper the primary radiation has only to pass the glass window, in which the main absorber is silicon (K rad. of 7 Å). The secondary radiation of the silicon is entirely absorbed in the Philite cap. The secondary radiation of the Philite cap itself, which consists of organic material, can be ignored. Therefore secondary radiation from the tube window in this type of tube does not occur.

Table III

Increase of dose rate due to secondary radiation from the wall of the applicator. Applicator: 10 mm Ø at 40 mm f. s. d.

Filter	0 Al (%)	1 Al (%)	2.5 Al (%)
None	100	100	100
Ni-plated	113	119	118
Ni-plated, lined with Al	106	106	105
Cr-plated	113	115	115
Cr-plated, lined with Al	103	100	100

Secondary radiation may also arise from the inside wall of the applicators. If the tube is used at 20 mm focus distance (fig. 9) only a rim of 1 mm of the applicator is exposed to the primary radiation, and the secondary radiation is negligible. However, when applicators for a focus-skin distance of 40 mm are used (fig. 1), a considerable area of these applicators is exposed to the primary beam and secondary radiation will originate from the wall of the applicator. The amount of scattered radiation was investigated using the flat chamber with the thin front face of 0.02 mm polystyrene. The results from a standard applicator giving a 10 mm circular field at a focus-skin distance of 40 mm are

summarized in table III. The brass applicator was either nickel- or chromium-plated or lined with a layer of 0.03 mm Al, as recommended by Zimmer (9). The aluminium absorbs the secondary radiation of the chromium or nickel. The secondary radiation of aluminium is only weak and moreover is readily absorbed in the air before reaching the skin.

The conclusion reached from these experiments is that the chromium-plated applicators are slightly better than nickel-plated ones. With chromium-plated applicators the dose rate caused by secondary radiation does not exceed 15 %. The secondary radiation is very soft and is almost entirely absorbed in 1 mm of water, as was shown by a comparison of depth-dose data using a nickel-plated applicator with those when an applicator covered with Al is used. Applicators for larger apertures are more favourable and show a smaller amount of secondary radiation. In most applications in contact-therapy the value of the permissible or desired surface dose is not very critical and therefore it is assumed that the slight amount of secondary radiation — never more than 15 % of the primary radiation — in this type of tube may be tolerated.

V. Roentgen ray protection

The tube is adequately shielded against the emission of primary radiation outside the useful beam. However, scattered radiation from the patient cannot be avoided.

The amount of stray radiation was determined when using the water-filled polystyrene tank as a phantom. The stray radiation was measured with the direct-reading dose meter, using a spherical ionization chamber of 4 cm cross section, filled with crypton of atmospheric pressure. The sensitivity of the instrument for the radiation qualities involved was determined by comparing it with a standard ionization chamber. The isodose surfaces are symmetrical around the axis of the tube. Their shape appeared to be to a large extent independent of the filter used and of the focus-skin distance. For all these measurements the full opening of the tube was used. Isodose curves in a plane through the axis of the tube are shown in fig. 10; the applicator with 20 mm Ø at 20 mm focus-skin distance was used without additional filter. The same curves may be used for other focus-skin distances and different filters if a suitable multiplication factor, which is given in table IV, is applied. From the data in table IV it follows that the multiplication factor depends mainly upon the filter and is practically independent of the focus-skin distance. The reason for this is that at a certain angular aperture the same total amount of radiation strikes the phantom and is scattered by it.

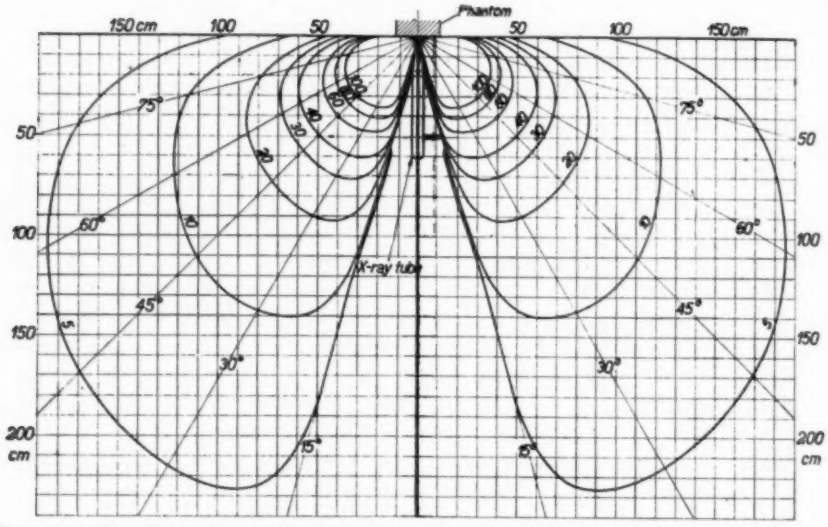

Fig. 10. Isodose curves around the tube of the stray radiation from a water phantom expressed in 10^{-5} r/sec or mr/1,000 r. To be used with the multiplication factors of Table IV. Cross-section field equal to focus-skin distance.

Table IV

Multiplication factors to be used with fig. 10.

Filter (mm Al)	F.S.D. (mm)	Multiplication factors	
		10^{-5} r/sec	mr/1,000 r
0	20	0.50	0.042
1.0	20	0.22	0.07
2.5	20	0.12	0.11
0	40	0.45	0.15
1	40	0.22	0.30
2.5	40	0.12	0.42
0	150	0.55	2.7
1	150	0.27	5.5
2.5	150	0.15	7.5

Thus roughly, but for the purpose sufficiently accurate, the multiplication factors are:

0.5 for 0.0 mm Al additional filter.
0.25 for 1.0 mm Al.
0.12 for 2.5 mm Al.

The amount of scattered radiation can also be expressed in terms of milliroentgen per 1,000 roentgen delivered to the patient. The corresponding multiplication factors, also to be used with the isodose curves shown in fig. 10, are given in the last column of table IV. The relative amount of scattered radiation increases as more filter is used (harder radiation).

Taking 0.3 r per week as the maximum permissible dose, in accordance with the new United States Handbook for Medical Roentgen Ray Protection, the isodose-surface marked 10 is safe during a total treatment time of 100 min per week, whereas in a plane through the handle of the tube this is decreased to 20 min per week in case no protective apron and gloves are worn. It should be noted that especially at a long focus-skin distance and with strong filtration the amount of scattered radiation per 1,000 r delivered increases rapidly.

The data given are maximum values; for fields smaller than the full opening 1 : 1 the amount of stray radiation will be reduced in proportion to the field area. The radiation safety can be considerably increased by using a round metal disc around the shield near the patient. In this way the comparatively safe region around the tube (without disc a cone with an angle of $2 \times 15°$) formed by the shadow of the shield and that of the applicator is widened. The stray radiation in a backward direction can be almost entirely eliminated by covering the skin with a lead foil having a hole slightly smaller than the aperture of the applicator, because then all backward scattered radiation has to pass through the wall of the applicator or the lead foil.

The author wishes to express his thanks to Mr J. PROPER for the skilful and conscientious way in which he assisted in carrying out these experiments.

SUMMARY

The various causes of errors in contact-therapy dosimetry are analysed and methods for avoiding these errors are described. Extensive measurements have been carried out with the Philips apparatus in regard to: the absorption characteristic of the radiation in aluminium, the half-value layer for different added filters, the field distribution where the effect of a compensating filter is described, the determination of depth-dose data and of isodose curves in a water phantom, the influence of secondary radiation from the applicators and the dose rate of the stray-radiation around the tube caused by scattering from the patient. A dynamic electrometer was used and proved to be very useful for this kind of work.

The results of the measurements are compared with those obtained by other authors.

ZUSAMMENFASSUNG

Die verschiedenen Fehlerquellen der Dosimetrie bei Kontaktbestrahlung werden besprochen und Methoden zur Vermeidung dieser Fehler beschrieben. Umfassende Messungen wurden mit dem Philips-Apparat vorgenommen, und zwar inbezug auf: die Absorptions-Charakteristik der Strahlung in Aluminium, die Halbwertschicht bei verschiedenen Zusatzfiltern, die Feldverteilung mit Beschreibung der Wirkung eines Ausgleichfilters, die Bestimmung der Tiefendosen und der Isodosenkurven in einem Wasserphantom, den Einfluss von Sekundärstrahlung der Tubusoberfläche, sowie auf die Menge der Streustrahlung um die Röhre herum durch Streuung seitens des Patienten. Ein dynamisches Elektrometer wurde benutzt und erwies sich bei Messungen dieser Art als überaus nützlich.

Die Ergebnisse der Messungen werden mit den von anderen Autoren erhaltenen verglichen.

RÉSUMÉ

Le present article analyse les différentes causes d'erreurs en dosimétrie de la therapie de contact et décrit les méthodes pour obvier à ces erreurs. Des mesures détaillées ont été effectuées avec l'appareil Philips concernant: les caractéristiques d'absorption du rayonnement dans l'aluminium, la couche de demi-absorption pour différents filtres additifs, la distribution par champ (avec la description des effets d'un filtre compensatoire), la détermination dans un phantome d'eau des caractéristiques de la dose en profondeur et des courbes d'isodoses, l'influence du rayonnement secondaire des localisateurs et enfin le pourcentage des radiations dispersées autour du tube par le malade lui-même. Un électromètre dynamique a été employé et son utilité pour ce genre de travail a été prouvée.

Le résultat des mesures a été comparé avec celui obtenu par d'autres auteurs.

REFERENCES

1. G. J. v. d. Plaats, Thesis. Utrecht 1938.
   D. den Hoed, Acta Rad. *19*, 239, 1938.
   U. Henschke, Strahlentherapie *68*, 90, 1940.
   C. B. Braestrup and I. H. Blatz, Radiology *35*, 198, 1940.
   L. F. Lamerton, Brit. J. Rad. *13*, 136, 1940.
   H. Smereker, Strahlentherapie *58*, 676, 1937.
   S. Hultberg, Acta Rad. Suppl. LIV, 1943.
   E. Quimby and E. F. Focht, Radiology *50*, 653, 1943.
2. H. Chaoul, T. Schatter and F. Wachsmann, Strahlentherapie *69*, 231, 1941.
3. Compare: J. Read, Brit. J. Rad. *22*, 349, 1949.
4. Compare: L. S. Taylor and G. Singer, Radiology *22*, 445, 1934.
   H. Behnken and H. Nitka, Phys. Z. *36*, 459, 1935.
5. J. van Hengel and W. J. Oosterkamp, Philips Techn. Rev. *10*, 338, 1949.
6. F. T. Farmer, Nature *150*, II, 521, 1942.
   F. C. Armistead, J. C. Pennock and L. W. Mead, Phys. Rev. *76*, 860, 1949.
7. P. Ott, Strahlentherapie *59*, 189, 1937.
8. W. J. Meredith, Brit. J. Rad. *13*, 320, 1940.
9. Th. Zimmer, Strahlentherapie *64*, 348, 1939.

FROM THE ROENTGEN DIAGNOSTIC DEPARTMENT OF KAROLINSKA SJUKHUSET (CHIEF: PROF. ÅKE ÅKERLUND) AND THE SURGICAL CLINIC OF THE ROYAL VETERINARY COLLEGE (CHIEF: PROF. GERHARD FORSSELL), STOCKHOLM, SWEDEN.

ROENTGENOLOGICAL STUDIES OF EXPERIMENTAL PULMONARY EMBOLISM WITHOUT COMPLICATING INFARCTION IN DOG[1]

by

Sven Roland Kjellberg and *Sten-Erik Olsson*

According to current opinion an obstructive embolus in the pulmonary artery of individuals with normal circulation does not give rise to any infarct. This is thought to be due to the double system of circulation; the bronchial arteries caring for the nutrient supply and the pulmonary for the gaseous exchange associated with respiration.

According to RAUBER and KOPSCH there exists in the human an extensive anastomosis between the two circulations which is partly arteriolar and partly capillary in nature. The investigations of GUILLOT and MILLER support this conception. According to ELLENBERGER and BAUM the anatomical conditions are analogous in domestic animals. STITZ on the other hand claims that the anastomoses are not present in the dog. ZIETSCHMANN (Ellenberger-Baum) questions Stitz's assertion and our investigations are also at variance with it.

Under normal circulatory conditions the double vascularisation prevents lung infarction even in a complete obstruction of the pulmonary artery. Infarction occurs only when there is cessation of circulation in the branches of the bronchial arteries as in cases of cardiac weakness, valvular defects or other associated disorders. CARLOTTI, HARDY, LINTON and WHITE think therefore that one must distinguish between pulmonary embolism and pulmonary infarction, because they are often not synonymous.

Although opinions differ, most authors claim that no roentgenological changes are observed in uncomplicated pulmonary embolism. On the

[1] Submitted for publication Jan. 28, 1950.

other hand, if the case is complicated by infarction marked changes are found. These are due mainly to diminished air content and decreased air entry caused by edema and haemorrhage. In a large number of cases a hydrothorax may develop as well.

In a paper published in 1938, re-emphasized by a publication in 1948, WESTERMARK claims, however, to be able to observe distinct and typical roentgenological changes even in uncomplicated pulmonary embolism, that is in cases without infarction. He is of the opinion that due to obstruction and irritation caused by the embolus the vessels are contracted and devoid of blood on the peripheral side of the embolus. Thus, the vascular design should totally or partly disappear on the roentgenogram, and the above mentioned area of the lung should be ischaemic. He writes on page 366: »In those cases showing lung embolism without infarction the ischaemia of the distributed area of the pulmonary artery on the peripheral side of the embolus or emboli has appeared on the radiogram as a local and well defined clarified zone with diminished or absent vascularisation. In an area corresponding to the site of the embolus and on the central side of this the vascular design has been well maintained but seems to stop abruptly. On account of the distribution of the arterial branches the clarified zone assumes the shape of a wedge with its apex directed towards the hilum and its base towards the periphery of the lung.»

SHAPIRO and RIGLER support this opinion in an article published in 1948. The figures reproduced in both articles however are of such a nature that there is no possibility for the reader to form an opinion regarding the accuracy of these observations. From the description, however, it appears that there are heart complications as well, in almost every case. As mentioned above, these complications cause a disturbance in the nutrition of the lung.

Considering, for many reasons, that it has not been clearly established that distinct changes are seen on the roentgenogram in uncomplicated pulmonary embolism we considered it of great interest to carefully investigate the subject by experimental-roentgenological studies in dogs. In order to have the picture undisturbed by cardiac complications, only healthy animals were used.

Material

Nine normal dogs of different breeds, varying from eight months to seven years in age, but predominantly of large size were used. Eight were subjected to roentgenological examination and in one the lung was examined by surgical exposure.

Methods

The dogs were anaesthetized with nembutal, intravenously, the dose varying with body weight. Immediately following anaesthetization the dogs were roentgenographed. All films were exposed without difficulty, at the end of inspiration, the respiration in all cases being quiet and slow. Roentgenograms were taken in anteroposterior, lateral and oblique projections. Satisfactory pictures having been obtained, the v. jugularis ext. was opened and the artificial embolus intended for the experiment in question was put in. The size of the embolus varied somewhat for different animals, but was always of a size just large enough to pass down the v. jugularis ext.

In four cases the embolus consisted of a glass cylinder specially constructed for this purpose and partly filled with barium sulphate. In four cases a substance which at body temperature is pliable and soft, but at room temperature is firm, was used. The composition of this medium was as follows:

Barii sulf.	10 gms
Paraffin liq.	15 »
Paraffin sol.	75 »
Cera alba	10 »
Adeps lanae	30 »

Using this material, pellets 3—4 cm long and of different widths were made. To prevent fragmentation each one was encased in a very thin rubber membrane. The soft consistency of the composition and the elasticity of the rubber made this artificial embolus very suitable for the purpose. This embolus not only obstructed the main vessels but also sent out small offshoots into the branches. (See fig. 3.)

In order to rapidly introduce the embolus into the circulation without alteration it was laid in a thin metal tube, of the same calibre as the vena jugularis ext. This was then put down into the vein and with a small piston the embolus was ejected into the blood stream, care being taken to prevent the introduction of air. In one case the composition was used without the membrane mentioned above and it divided into small fragments and was not suitable for the study of circulatory disturbances in the larger branches of the pulmonary artery. In a second case the chest was opened and a study was made of the lungs before and after the introduction of the embolus. During the whole time of the latter experiment respiration was maintained with the aid of additional pressure in the usual way. The time of observation was about four hours. In order to

Fig. 1. The lungs of dog no. 7.

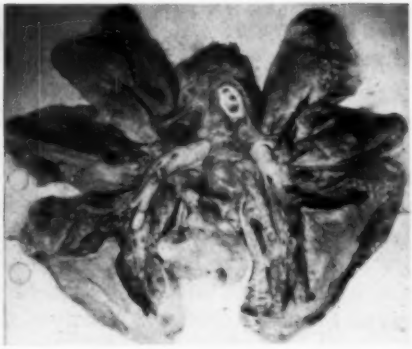

Fig. 2. Pulmonary arteries split open.

Fig. 3. Enlargement of the right pulmonary artery.

Fig. 4. Detail of the embolus.

roentgenologically verify that the obstruction was complete a contrast-medium (thorotrast) was injected in one case after the embolus was lodged. Post mortem examination was made in all cases, the site of the embolus determined, and its obstructive character verified.

Fig. 5. A.-p. view of chest before pulmonary embolism.

Fig. 6. A.-p. view of chest after pulmonary embolism.

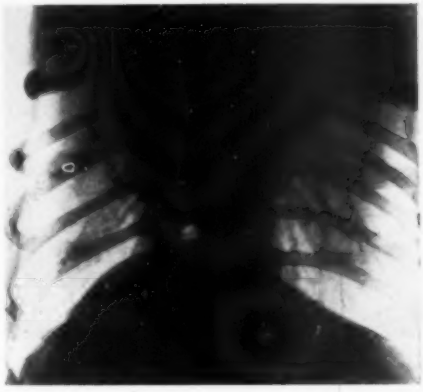

Fig. 7. Detail of roentgenfilm in fig. 1 e.

Results

Of the eight cases examined, none showed any changes on the roentgenogram after the lodging of the embolus. The vascular design was equally prominent on both sides, both before and after the embolic phenomenon. Neither appreciable diminution in the calibre of the artery

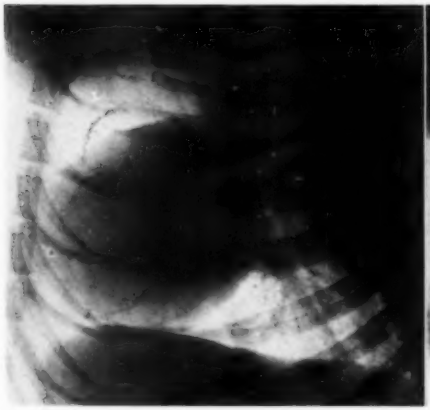

Fig. 8. Lateral view of the chest before pulmonary embolism.

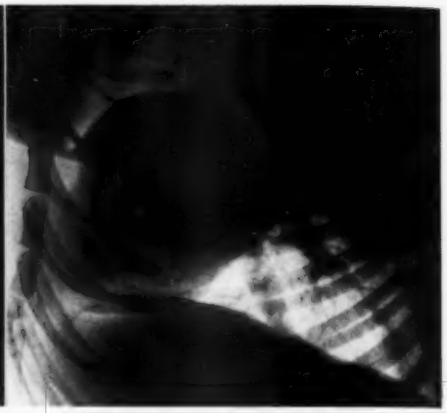

Fig. 9. Lateral view of chest after pulmonary embolism.

Fig. 10. Oblique view of chest before pulmonary embolism, dog no. 3.

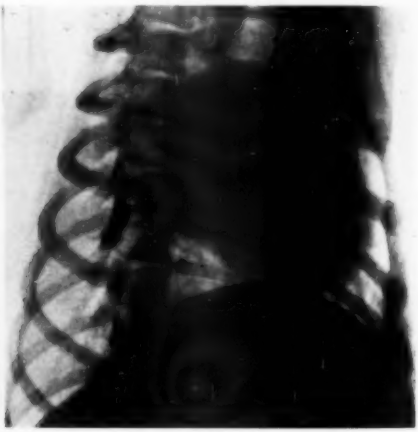

Fig. 11. Oblique view of chest after pulmonary embolism.

on the peripheral side of the embolus, nor any abrupt stop of the vascular design was seen. No local emphysema or other lung changes were seen. In all cases the time of observation was 2—4 hours after the embolus was at rest. (See figs. 1—11.)

In one case, where a contrast medium was injected after the introduction of the artificial embolus, a distinct difference between the vascular design within the blocked area and the rest of the lungs was ob-

served. The vascular design of the area in question was considerably finer and the vessels were less prominent depending on the degree of decreased filling with blood borne contrast in the branches on the peripheral side of the embolus.

At autopsy it was shown that the embolus was well fixed and on attempts to dislodge it back into the heart the intima followed. No difference in vascularisation of the lung was observed except in one case where a few small areas, pale and with a slight hyperaemic border could be seen. Histologically no infarct could be identified. The branches of the pulmonary artery on the peripheral side of the embolus were not contracted. They contained about the same quantity of blood as the other vessels.

In one case where the chest was opened and the lungs were studied in situ and respiration was continued with additional pressure no changes could be seen after the introduction of the embolus. The colour was unaltered within all the lobes of the lung and the production of any local emphysema could not be observed.

In summary it can be stated that our investigations support the current opinion that no roentgenological changes in the lungs are observed in uncomplicated pulmonary embolism. Further, it can be stated that no infarction will occur as long as the circulation through the bronchial artery is undisturbed.

SUMMARY

The authors have experimentally caused pulmonary embolism in dogs. They have not observed any roentgenological changes whithin the lung fields in cases with normal circulation.

ZUSAMMENFASSUNG

Die Verff. haben an Hunden experimentell Lungembolie erzeugt. Bei Fällen mit normalen Kreislauf haben sie in den Lungenfeldern keinerlei röntgenologische Veränderungen beobachtet.

RÉSUMÉ

Les auteurs ont provoqué des embolies pulmonaires expérimentales chez des chiens. Ils n'ont observé aucune modification roentgenologique au niveau des champs pulmonaires dans les cas où la circulation était normale.

REFERENCES

CARLOTTI, HARDY, LINTON, WHITE: J.A.M.A. 134: 1447, 1947.
ELLENBERGER, BAUM: Handbuch der vergleichenden Anatomie der Haustiere. Berlin 1943.
GUILLOT: Cited by Miller.
MILLER: The Lung. Sec. Ed. Springfield 1947.
RAUBER, KOPSCH: Lehrbuch und Atlas der Anatomie, Band II. 1941.
SHAPIRO, RIGLER: Am. J. Roentg. 60: 460, 1948.
STITZ: Anatomische Untersuchungen über den Verlauf der Aa. und Vv. bronchiales des Hundes und über ihre Anastomosen mit dem Pulmonalgefäss-system. Diss. Hannover 1936.
WESTERMARK: Acta Radiol. 19: 357, 1938.
— Roentgen studies of the lungs and heart. Univ. Minnesota Press. 1948.

FROM THE NORWEGIAN RADIUM HOSPITAL, OSLO, NORWAY
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MULTIPLE MYELOMA[1]

by

Lars Anda

A series of multiple myeloma observed at the Norwegian Radium Hospital has been studied in an effort to elucidate the question as to whether roentgenologic examination of the skeleton may yield conclusive or useful diagnostic information. Further, the results as obtained with irradiation have been studied.

The roentgenologic features in multiple myeloma vary. According to AEGERTER and ROBBINS (1), at least three clinical varieties of the disease can be recognized. A similar classification seems applicable also to the roentgenographic changes. The varieties mentioned are as follows:

I. A diffuse osteoporotic type without localized nodules. In this variety the myeloma is so generalized early in the disease that all red marrow must be considered as affected simultaneously. This type is regarded as the rarest variety. In a series reported by BAYRD and HECK (2) it occurred in 9 per cent of the cases. In the same series, 12 per cent of the cases presented no visible bone abnormalities.

II. A classical type which takes the appearance of multiple tumors of the skeletal system. These tumors occur predominantly in flat bones and in the metaphyses of the long bones, a feature which previously was regarded as characteristic of multiple myeloma. BAYRD and HECK (2) found multiple foci in the bones in 78 per cent of the cases in their series, while JAFFE and LICHTENSTEIN (14) maintain that the classical features are rather an exception than a rule.

III. A solitary type. Multiple myeloma often begins as a single focus which within a comparatively short time spreads to the entire skeleton. In rare instances the process may remain solitary for years or decades before spread ensues. Two subtypes have been described (13, 17, 25, 32):

[1] Submitted for publication Febr. 15, 1950.

a) A cystic trabecular type resembling the benign giant-cell tumor of bone. This appears as a sharply demarcated circular area of destruction with coarse irregular trabeculae.

b) An osteolytic type with destructive lesions resembling cancer metastases.

Regarding the treatment, irradiation with roentgen rays has so far been the only useful form of therapy which can be offered these patients according to the general belief that multiple myeloma was highly radiosensitive.

GARLAND and KENNEDY (11), who in 1947 studied a series of 13 cases treated at the San Francisco Hospital, reached a somewhat different conclusion. They point out that the effect of roentgen treatment of multiple myeloma has not been thoroughly investigated except by a few authors. Most authors stop with the statement that multiple myeloma is a highly radiosensitive lesion, but give no really convincing evidence with which to support it. There are, however, some fairly complete references in the literature to solitary myelomas treated with roentgen rays, and most authors agree that these tumors are radiosensitive and even radiocurable in certain instances.

In GARLAND and KENNEDY's series of 13 cases treated at the San Francisco Hospital, improvement was noted in 6 cases, 6 were not appreciably benefited, and 1 had incomplete treatment. One patient survived over 9 years. The average survival for the remaining cases was 10.4 months. The authors conclude that multiple myeloma is not a very radiosensitive disease, and that it is by far as radiosensitive as generally believed.

Author's Series

The present series comprises 11 cases, 8 men and 3 women, of histologically verified cases of multiple myeloma and 1 case of »solitary myeloma» treated at Norwegian Radium Hospital during the ten-year period from 1938 to 1948. The ages of the patients when the diagnosis was made, ranged from 47 to 72 years, averaging 60 years. The age of the patient with »solitary myeloma» was 42 years.

The predominant symptoms were pain, malaise, and loss of weight. Pathological fracture was an early feature in 3 cases, paraplegia in 1. The severity of the symptoms varied. The average duration of symptoms from the time of their onset until the patient sought medical advice was ten months, ranging from two months to two years.

A classification of the series according to AEGERTER and ROBBINS has been attempted (table 1). An exact grouping, however, is not feasible.

Fig. 1. Male, aged 61. Large tumor of the chest wall, situated anteriorly to the left, with an even, rounded contour.

Fig. 2. Same patient. Better exposed films showing expansive lesion on the 7th rib with irregular cystic structure. Operative defect with regeneration of bone in the left 8th rib.

Table 1

Multiple Myeloma. D.N.R. 1938—1948

Case	Subtype	Area
1	Multiple Focal (Diffuse)	All Red Marrow
2	Multiple Focal (Diffuse)	All Red Marrow
3	Multiple Focal	Thorax, Skull
4	Multiple Focal	Flat Bones
5	Solitary then Multiple	R. Humerus R. Ulna, Skull
6	» » »	Clavicula, Costa
7	» » »	Columna
8	» » »	Columna, Skull
9	» » »	L. Femur
10	» » »	R. Femur
11	» » »	R. Femur
12	Solitary	Pelvis

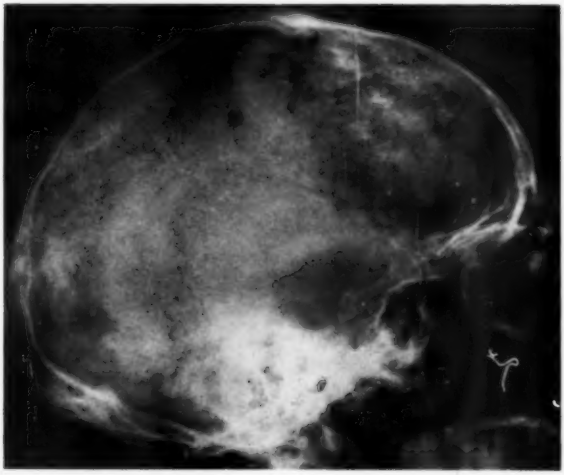

Fig. 3. Male, aged 61. Multiple foci in the skull.

The diffuse osteoporotic type did not occur in the present series, though there were 2 cases (cases 1 and 2) representing borderline cases between this type and the classical type (type II).

The classical type occurred in 2 cases. According to AEGERTER and ROBBINS (1) this type must be termed multiple focal. Figures 3 and 4 show the changes in the cranium in these patients.

The solitary type with subsequent multiple development occurred in 7 cases. The primary focus was remarkably often situated in the extremities, viz. in the femur in 3 cases (fig. 5) and in the humerus in 1 case.

The lesions were of the cystic trabecular type in 2 cases with general involvement, and in an additional case (case 12), while they were of a more elusive or osteolytic type in the remaining cases. The spread generally occurred after a varying length of time. In 1 case (case 5) it did not occur until after a period of seven years, and in another (case 12) with a large but localised lesion in the pelvis, spread has not yet occurred after an observation period of approximately four years.

From what has been said it seems evident that not much can be concluded merely on the basis of the roentgenologic findings. A probable diagnosis of multiple myeloma seems justified only in a limited number of cases of the classical type and in the advanced stages of the disease. Otherwise, other factors and methods of examination of interest in multiple myeloma must be considered. These are briefly: changes in the blood,

Fig. 4. Female, aged 68. Large irregular, but well-defined destructive lesion in the region of the forehead. Some similar smaller defects in the skull.

Fig. 5. Male, aged 66. Large irregular, but sharply outlined rarefaction in the proximal end of the shaft of the femur. No expansion of bone, no periosteal reaction.

viz. hyperproteinemia, hyperglobulinemia, hypercalcemia (in about 50 per cent) and the demonstration of myelomatous changes in the sternal marrow or in biopsy specimens from foci in the bones.

Serum Proteins. Serum proteins were determined in 5 cases. Hyperproteinemia was not present in any of these cases. The globulin content, however, was comparatively high, with an albumin-globulin fraction varying from 0.93 to 1.27, while normal values range from 1.7 to 3. Bence-Jones protein was present in 1 case (case 1), absent in another (case 9). Moreover, the sedimentation rate may to a certain extent reveal information about the globulin content. In the present series the sedimentation rate was considerably increased in most cases, in 1 case (case 3) up to 115 mm/1 hour. On the other hand, in 3 cases of the solitary type with subsequent spread (cases 5, 9 and 11), it was remarkably low, viz. 9 mm, 10 mm, and 4 mm respectively.

The calcium content in the blood as determined in 2 cases was not increased.

Bence-Jones protein was looked for in 10 cases but found in only 2.

Sternal smears were examined in 9 cases. Typical collections of plasma cells were present in 6 cases. Collections of myeloma cells were reported in 1 case. In 3 cases of the »solitary type» (cases 5, 10 and 12) no myelomatous changes could be demonstrated. Several smears were made in 2 of these cases.

Biopsy. In the event of negative sternal smears, a needle biopsy of a bone focus may give tangible evidence of the true nature of the lesion.

In the present series, needle biopsy was performed in 10 cases, in most of which the histologic diagnosis was plasmocytoma. In 2 cases (cases 6 and 10) the histologic findings were described as tumor tissue composed of myeloma cells.

As to the microscopic appearance, reference is made to the special literature. (7, 11, 15, 17, 26, 28.)

The differential diagnosis may vary according to the type of lesion actually present. The diffuse osteoporotic variety may be difficult to distinguish from other diseases associated with osteoporosis *e. g.* hyperparathyroidism and other endocrine disorders, syphilis, and diffuse carcinomatosis.

In the presence of a more classical manifestation of multiple myeloma, roentgenograms may be highly suggestive, but not necessarily conclusive, as diagnostic difficulties may arise in distinguishing the lesions from cancer metastases, osteolytic sarcoma, lymphoblastoma, and lymphogranulomatosis.

However, if these various possibilities are considered and the procedures mentioned are undertaken, a correct diagnostic result will usually be obtained.

The solitary types may be hard to distinguish from innocent giant-cell tumours, solitary cysts of bone, solitary cancer metastases, metastases of hypernephroma, and lipoid granuloma. Needle biopsy, however, in most instances gives tangible evidence as to the nature of the lesion.

Treatment. Roentgen treatment was instituted in all cases in the present series. The physical factors were as follows: 175 Kv, 4 Ma, target-skin distance 50 cm, filtration 1 mm Cu. The field size varied from 7 by 10 cm to 18 by 25 cm. Total irradiation was given in 1 case. Large doses were used, usually 350 r daily.

Otherwise various data of therapeutic importance are shown in table 2. The results of irradiation have been classified as: subjective improvement, objective improvement, and no effect. Subjective improvement with alleviation of pain resulted in 5 cases, while objective improvement occurred in 3. No apparent improvement was found in 4 cases. The average survival following treatment was twenty months for the entire series.

Table II

Cases of Multiple Myeloma Treated by X-Rays. (D.N.R. 1938—1948.)

Case	Sex	Age	Total Dosage (r skin)	Results	Survival
1	M	66	3,500 r to lumbar spine, in 10 days	Subj. improvem.	13 mo.
2	M	72	600 r total body irrad. in 20 d.	No change	1 mo. 10 d.
3	M	61	2,600 r × 2 to thorax, in 26 days.....	Subj. improvem.	4 mo.
4	F	68	May 1944 3,100 r to right lat. skull, in 25 days..... 2,850 r to central skull,	No change	6 mo. 10 d.
			June 1944 2,850 r to thoracal spine, in 9 d. ..... 3,300 r to right knee, in 12 d.	No change	
5	M	47	May 1940 3,000 r × 2 to r. humerus, in 30 d.	Obj. improvem.	103 mo.
			May 1948 3,500 r to r. humerus, in 10 d. ..... 3,500 r to l. antebrach. in 10 d.	Subj. improvem.	
6	M	53	4,000 r to right clavic. in 20 d.	Obj. improvem.	62 mo.
7	M	49	3,500 r to thoracal spine, in 10 d.	No change	5 mo. 9 d.
8	F	66	3,500 r to spine in 10 days ..... 3,500 r to r. frontal bone, in 10 d.	Subj. improvem.	46 mo.
9	M	57	2,800 r to left hip, in 8 d. ..... 1,050 r to sternum, in 3 d. ..... 1,400 r to left femur, in 4 d.....	No change	15 d.
10	F	61	3,500 r × 3 to r. femur, in 30 d.	Subj. improvem.	6 mo. 15 d.
11	M	66	3,500 r × 2 to r. femur, in 20 d. ..... 3,500 r to r. hip, in 10 d.	No change	9 mo. 15 d.
12	M	42	3,500 r to right pelvis, in 30 d.	Obj. improvem.	Still living (over 3 years).

Considering the results obtained in the various groups according to type those obtained in the combined group of diffuse osteoporotic myeloma and the classical type were as follows: Subjective improvement in 2 cases and no improvement in 2 cases. The average survival following treatment in this group was six months.

In the group of solitary myeloma with subsequent spread, objective improvement was observed in 2 cases (cases 5 and 6), subjective improvement in 2 (cases 8 and 10), and no improvement in 3 cases (cases 7, 9 and 11). The average survival following treatment in this group was two years and eight months. Case 5 is still alive eight years and seven months after the treatment, though multiple foci are now present. Case 6 died five years and two months after the treatment. Case 9 was highly exhausted at the time of admission so that the treatment had to be abandoned after only a few small doses.

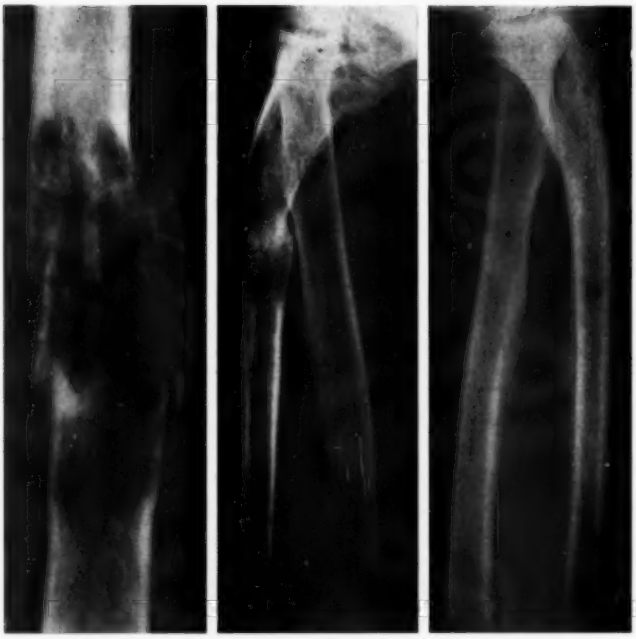

Fig. 6. Fig. 7. Fig. 8.

Fig. 6. Male, aged 47. Pathological fracture of femur and an irregular area of destruction, 10 cm long, at the fracture site. Slight expansion of the bone with cystic radiotranslucencies and irregular trabeculae. Rarefaction with partial destruction of the cortex.

Fig. 7. Fracture of proximal portion of ulna and irregular area of destruction at fracture site.

Fig. 8. Same patient. Sharply demarcated circular defect in right temporal bone.

Finally there is case 12 in which more than three years after the treatment the lesion still persists as a solitary myeloma without signs of further spread.

Regarding the radiosensitiveness of the disease the present series is too small to allow definite conclusions, particularly where a lesion which runs such a capricious course as myeloma is concerned. The results of treatment must be seen in relation to the various roentgenologic and anatomic features. Thus evaluated the present series seems to indicate that »solitary myeloma» is the most radiosensitive type which may be radiocontrollable in certain instances. Vigorous irradiation, however, is necessary.

The radioresponsiveness of the multiple types obviously varies.

Fig. 9. Multiple foci in the skull.

Report of Cases

Two cases, viz. cases 5 and 12, merit special attention:

Case 5. T. T., a 47-year-old truckdriver, was admitted into the Norwegian Radium Hospital on April 4. 1940 following a spontaneous fracture of the left upper arm. Roentgenographic examination on admission showed a pathologic fracture of the shaft of the humerus (fig. 6). An irregular area of destruction about 10 cm long involving the spongiosa, was even about the fracture site. Roentgenographic examination of the rest of the skeleton was negative. A sternal smear was normal. The sedimentation rate was 9 mm. Albumin was not present in the urine.

Roentgen treatment was instituted and consisted of 3,000 r each to two fields in thirty days.

Partial recalcification and considerable improvement were observed. However, later attemps at reducing the fracture were unsuccessful and resulted in the formation of a pseudarthrosis with considerable functional impairment.

On December 1, 1947, spontaneous fracture of the right ulna occurred, and the patient was readmitted into the Norwegian Radium Hospital on April 8, 1948. Roentgenographic examination (fig. 7) showed a cystic lesion and pseudarthrosis of the right ulna, and a cystic lesion in the left ulna (fig. 8). No swelling or periosteal reaction could be demonstrated.

Laboratory Data

Sedimentation rate 11 mm, total blood proteins 8 Gm/100 ml (albumin 4 1 Gm/100 ml, globulin 3.59 Gm/100 ml), serum calcium 9.7 mg/100 ml, rest-N 16.1 mg/100 ml, no albuminuria.

Examination of a biopsy specimen from the right ulna revealed plasmocytoma (Dr. R. Eker, Oslo, Dr. L. Santesson, Stockholm), photomicrograph I.

A sternal smear showed no evidence of myelomatosis (Dr. R. Eker, Dr. C. Müller).

Roentgen treatment was instituted and consisted of 3,500 r each to the right and left forearms.

Fig. 10. Male, aged 42. Large, irregular, sharply demarcated area of destruction in the right ilium, right acetabular region, right pubic bone, left acetabular region, and left pubic bone.

On July 29, 1948 the patient was readmitted for the second time because of a tumor of the anterior wall of the right exterior auditory canal.

Roentgenographic examination showed considerable destruction of the right temporal bone above and behind the maxillary joint. A number of sharply demarcated circular radiotranslucencies were also seen in other bones (fig. 9).

Examination of a biopsy specimen from the right temporal bone showed plasmocytoma.

A sternal smear was negative.

Treatment with N-mustard gas (Nitracin 7.3 mg × 4) was instituted.

Progression of the destruction was noted, and irradiation was therefore instituted. The patient complained of pain in various places. However, his weight increased, and he was otherwise in comparatively good condition.

The present case demonstrates a »solitary myeloma» with subsequent spread to other bones after more than seven years. Roentgen treatment in this case temporarily delayed progression. A peculiar feature, however, is that no changes of the sternal marrow have so far been demonstrated.

Case 12. H. E., a 42-year-old man, was admitted into the Norwegian Radium Hospital on October 12, 1945, because of a rarefaction in the right ilium. A needle biopsy specimen taken previously and examined at the Department of pathology of the University of Oslo showed Ewing's sarcoma or lymphosarcoma.

Roentgenographic examination on admission showed extensive destruction of the lateral portion of the ilium extending to the acetabular region and towards the base of the pubic bone. The lesion appeared as a large irregular, but well-defined radiolucency

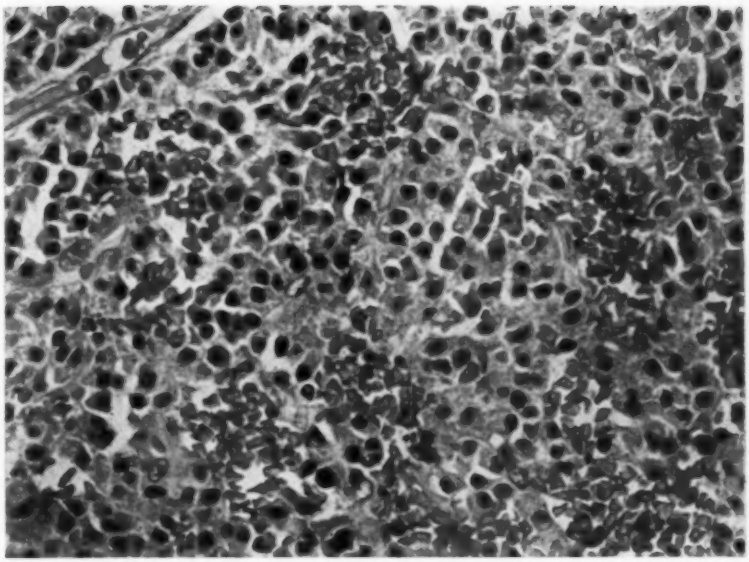

Fig. 11. Cellular tumor tissue composed of closely packed, round-oval or polyhedral cells with eccentrically placed nuclei. Chromatin collected in small masses around the periphery of the nucleus like the figures on a clock-face.

with irregular trabeculae. Similar destructive lesions were seen in the left pubic bone and in the acetabular region. The sedimentation rate was 63 mm. Albuminuria was present, but no Bence-Jones protein.

A needle biopsy showed a possible Ewing sarcoma or a possible myeloma. A sternal smear was negative.

Roentgen treatment was instituted, and consisted of 3,500 r each to three fields. Improvement was observed. The patient was readmitted on June 17, 1948. Roentgenographic examination of the pelvis showed unchanged conditions, and no changes were revealed in the rest of the skeleton. Laboratory data: Sedimentation rate 63 mm, total blood proteins 7.15 Gm/100 ml (albumin 4.16 Gm, globulin 2.99 Gm, albumin-globulin fraction 1.39), non protein nitrogen 17.8 mg/100 ml, calcium 9.2 mg/100 ml, phosphorus 3.1 mg/100 ml, cholesterol 317 mg/100 ml and 496 mg/100 ml, no albuminuria.

Examination of several biopsy specimens from the right ilium showed merely fibrous tissue and fat tissue. Sternal smears were all negative. Bence-Jones protein was not present.

Certain features in this case indicated the possibility of Schüller-Christian's disease. Tumor tissue, however, was definitely present in the first biopsy specimen, while no granulation tissue could be detected (Fig. 11).

Reexamination of the specimen gave conclusive evidence of plasmocytoma (Dr. Eker). (Fig. 12.)

A »solitary myeloma» was thus present in this case for which reason it could not be included in the general group. However, it still represents

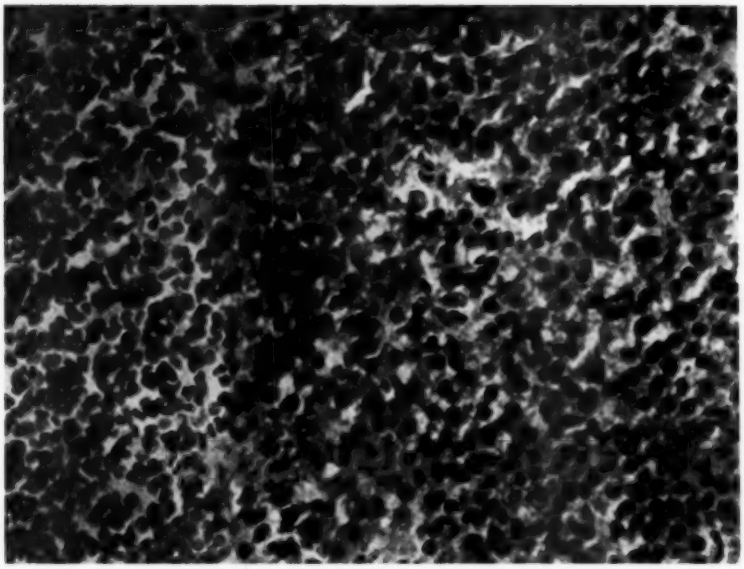

Fig. 12. Cellular tumor tissue composed of sharply outlined cells with eccentricity of nucleus. Many cells showing clock-face markings.

borderline case. Roentgenographic examination showed extensive destructive involvement of the pelvis and radiolucencies in several bones. »Solitary myeloma» and multiple types no doubt represent merely two different phases of the same process.

Biopsy specimens taken at different intervals after irradiation all showed a hypocellular fibrous tissue, indicating destruction of the tumor tissue in response to the irradiation. Still subsequent spread may be considered as likely to occur, though a few cases of complete cure, or absence of recurrence for up to twenty years, have been reported.

No cause, however, could be found as to the hypercholesterolemia, which thus might be considered an essential hypercholesterolemia.

Conclusion

On the basis of the present series, and conclusions drawn by other authors (2, 12, 17, 20), the author concludes that definite roentgenologic information is obtainable merely in certain far advanced cases or in classical cases with multiple manifestations. The roentgenographic findings are often uncharacteristic, and a definite diagnosis can only be established by means of supporting biochemical examinations, study of

sternal smears and biopsy specimens obtained directly from a focus in the bone.

The radioresponsiveness of the disease apparently varies. Results must consequently be evaluated by the roentgenologic and anatomic features. The average period of survival after treatment in the present series was twenty-three months. The comparatively long survival time observed in the present series is probably due to the high incidence of »solitary myeloma» with subsequent spread. The results as observed in this series indicate that solitary types are radiosensitive and even radiocurable in some instances. The evaluation of the results, however, may be complicated by the fact that »solitary myeloma» runs a most capricious, often tardy course, the reason for which is not revealed by histologic studies.

In one case with »solitary myeloma» where no evidence of spread could be detected three years after the treatment, repeated biopsies did not produce any evidence whatsoever of remnants of tumor tissue.

SUMMARY

During the period from 1938 to 1948, 11 cases of multiple myeloma and 1 case of »solitary myeloma», all verified by sternal puncture or biopsy, were treated at the Norwegian Radium Hospital. This series has been studied in an effort to elucidate to what extent roentgenographic examination may yield conclusive information on the diagnosis, and also to ascertain the effect of roentgen treatment.

Objective inprovement was observed in 2 cases, subjective improvement in 5 cases, and no improvement in 3 cases, following irradiation. Incomplete treatment was given in 1 case.

ZUSAMMENFASSUNG

In der Zeitspanne 1938—1948 wurden in der Norwegischen Radiumhospital 11 Fälle von multiplem Myelom und 1 Fall von »solitärem Myelom» behandelt, alle durch Sternalpunktion oder Biopsie bestätigt. Diese Reihe wurde studiert, um zu versuchen klarzulegen, in welchem Aussmasse die Röntgenuntersuchung für die Diagnose ausschlaggebende Auskünfte geben kann, sowie auch um die Wirkung der Röntgenbehandlung festzustellen.

Objektive Besserung nach der Bestrahlung wurde in 2 Fällen gefunden, subjektive Besserung in 5 Fällen und keine Besserung in 3 Fällen. In 1 Falle war die Behandlung unvollständig gewesen.

RÉSUMÉ

De 1938 à 1948 on a traité, à l'Hôpital Norvégien du Radium, 11 cas de myélomes multiples et un cas de »myélome solitaire», tous vérifiés par ponction sternale ou biopsie. Dans l'étude de cette série on s'est efforcé de tirer au clair jusqu'à quel point l'examen radiologique peut apporter des données décisives pour le diagnostic, et aussi de connaître l'effet du traitement par les rayons de Roentgen.

A la suite de l'irradiation l'amélioration était de nature objective dans deux cas, d'ordre subjectif dans 5, et dans 3 elle fut nulle. Un cas n'a reçu qu'un traitement incomplet.

REFERENCES

1. Aegerter, E. and Robbins, R.: Am. J. M. Sc. 213: 282—89: 1947.
2. Bayrd, E. D. and Heck, F. J.: J. A. M. A. 133: 147—57: 1947.
3. Bichel, J.: Acta Rad. 30: 49—63: 1948.
4. Bichel, J. and Kirketerp, P.: Acta Rad. 19: 487—503: 1938.
5. Blum, S. D.: Am. J. Roentgen. 57: 239—247: 1947.
6. Bull Engelstad, R.: Stråleterapi, J. Grundt Tanum, Oslo, 1946.
7. Court, J. S.: Am. J. Clin. Path. 16: 213—18: 1946.
8. Eposito, J. J.: Radiology. 40: 195—97: 1943.
9. Figi, Fr. A., Broders, A. C. and Havens, F. Z.: An. of Otol. Rhin. et Lar. 54: 382— : 1945.
10. Flink, E.: Radiology 50: 72—83: 1948.
11. Garland, L. H. and Kennedy, R. Bayles: Radiology 50: 297—317: 1948.
12. Geschickter, Ch. F. and Copeland, M. M.: Tumors of Bones, Am. J. Cancer. New York City 1931.
13. Gootnick, L. T.: Radiology 45: 385—391: 1945.
14. Harding, W. G. and Kimball, Th. S.: Am. J. Cancer 16: 1184—92: 1932.
15. Herbut, P. A. and Lowel, A. Erf.: Am. J. Clin. Path. 16: 13—21: 1946.
16. Howes, W. E. and Schenck, S. G.: Radiology 37: 18—34: 1941.
17. Jaffe, H. L. and Lichtenstein, L.: Arch. Path. 44: 207—46: 1947.
18. Jane, H. A.: Radiology 30: 94—109: 1938.
19. Janson, G.: Acta Rad. 27: 73—80: 1946.
20. Kiney, L.: Radiology 35: 667—75: 1940.
21. Marquis, W. J.: Am. J. Roentgen. 44: 858—65: 1940.
22. Mattich, W. L. and Thibaudeau: Am. J. Cancer 23: 513—21: 1935.
23. Morisette, L. and Watkins, Ch.: Proc. of The Staffm. of The Mayo Clin. 17: 433— : 1942.
24. Nielsen, H.: Nordisk Medicin 4: 3240— : 1939.
25. Paul, L. W. and Pohle, E. A.: Radiology 35: 651—66: 1940.
26. Rupert, A. W.: Arch. Path. et Bact. 53: 78—85: 1941.
27. Scott, E., Stanton, F. M. and Oliver, M.: Am. J. Cancer 17: 682—98: 1933.
28. Schwartz, St. O., Armstrong, B. E., Loeffler, E. and Mavrelis, W.: Arch. Path. 45: 380—384: 1948.
29. Snapper, I.: Med. Clinics on Bone Diseases, Intersc. Publishers, Inc. 1943 pp. 181—211.
30. Snapper, I.: J. A. M. A. 137: 513—16: 1948.
31. Tarr, L. and Ferris, H. W.: Arch. Int. Med. 64: 820—33: 1939.
32. Toth, B. J. and Wintermantel: Radiology 41: 472—79: 1943.
33. Ulrich, H.: Arch. Int. Med. 64: 994—1016: 1939.
34. Waldenström, J.: Acta Chir. Scand. 87: 365—79: 1942.
35. Wolf, E. and Nolan, L. E.: Radiology 42: 76—79: 1944.
36. Wood, H., Quinlan, J. W. and Merrit, E. F.: Am. J. Roentgen. 53: 466—69: 1945.

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ON THE DIAGNOSIS OF ATRESIA OF THE ESOPHAGUS[1]

Report of a Case

by

Sigurd Eek, Leif Efskind and *Aage Wolff*

Congenital atresia of the esophagus was regarded as fatal until LADD (1939) performed the first successful operation. He used the indirect method of establishing the esophageal anastomosis. LANMAN (1936) was the first to try primary anastomosis of the two esophageal segments, and HAIGHT (1941) reported the first successful case treated by this direct extrapleural method. His technique, with some modifications, has later been used by most surgeons. A great many varieties of atresia of the esophagus have been described. To VOGT's (1929) classification of atresia, which so far has been generally adopted, an additional developmental anomaly may be added, viz. that described by O'BANNON in 1946 (fig. 1, IV).

The roentgenological examination in atresia of the esophagus has been described in detail by HOLT, HAIGHT and HODGES in a publication in 1946. They consider roentgenological examination after ingestion of small amounts of iodized oil to be superior to other methods. This method, they claim, yields adequate diagnostic and topographic information. Methods — without use of contrast medium — have been described *e. g.* by SELANDER, by which the dilated, blind upper esophageal segment, which compresses and displaces the trachea anteriorly, is demonstrable in type III B atresia. SOLIS-COHEN and LEVIN claim to be able to diagnose this type of atresia by demonstration of a narrow airway passing from the trachea downwards to the stomach, representing the airfilled lower esophageal segment. FUHRMAN et al. insert a catheter

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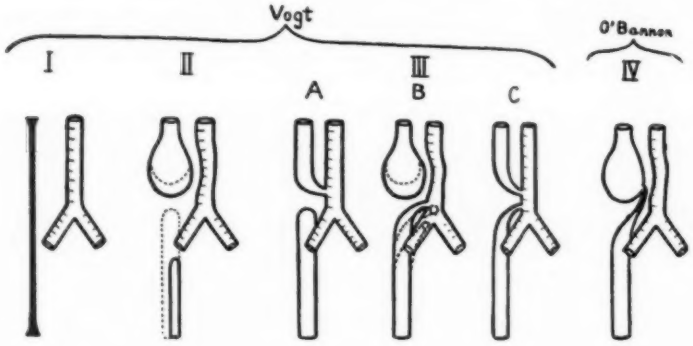

Fig. 1. Classification according to VOGT with an additional fourth type described by O'BANNON. Type III B constitutes 80—90 per cent of all cases, type II 5—10 per cent, while the other types are far more rare. The tracheo-esophageal fistula in type III B is usually situated $^1/_2$—1 cm above the carina, but may open into the carina or into one of the main bronchi, as a rule the right.

into the upper blind pouch. After this pouch has been expanded with air it appears as an airfilled cavity, frequently with a fluid level at the bottom.

Atresia of the esophagus generally is easily recognized on the basis of clinical and roentgenological findings. The differentiation of the various types of atresia, however, which is of essential importance to the surgical treatment, may not be so simple. Below a case is reported in which roentgenological examination with contrast medium revealed some peculiar features.

Case Report

The patient, a male child, 3 days old, had since birth presented the usual symptoms of atresia of the esophagus. Roentgenograms taken before admission, showed the characteristic blind pouch in the upper part of the mediastinum. The trachea was compressed and displaced anteriorly. Air as well as contrast medium was seen both in the stomach and in the small bowel. In spite of the fact that the contrast medium had not been aspirated after the first roentgenological exposure, no contrast medium could be seen in the bronchial tree or in the trachea. The lungs showed no signs of atelectasis or inflammation (fig. 2).

Fresh roentgenograms (Fig. 3) taken after admission into the University Hospital showed a narrow, airfilled passage between the trachea and the stomach, as described by SOLIS-COHEN and LEVIN, and the atresia was interpreted as VOGT's type III B. The operation showed an atresia of the type presumed. The distance between the two esophageal segments was about 4 cm. A primary anastomosis was established, though this procedure involved a considerable tension on the sutures. The postoperative course was

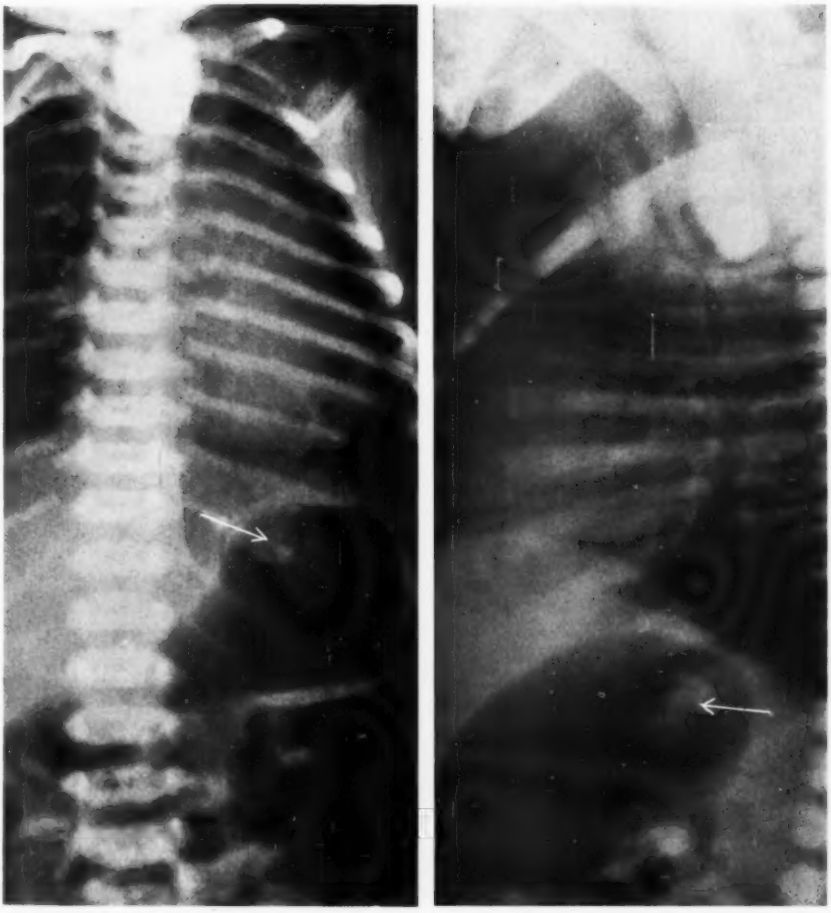

Fig. 2 a. Fig. 2 b.

Fig. 2. a) The contrast medium is seen in the upper blind esophageal segment, and in the stomach and small intestine. *No contrast medium in the bronchial tree.* b) Upper blind segment of the esophagus filled with contrast medium and air. The trachea is slightly compressed in the anterio-posterior plane, and displaced anteriorly.

complicated by esophageal fistula, which occurred on the eleventh day. To facilitate healing of the fistula, gastrostomy was performed and maintained for four weeks. Otherwise the postoperative course was uvenentful. A narrowing of the esophagus at the site of the anastomosis occurred, but was easily controlled by dilatation. Roentgenograms at the time of discharge showed satisfactory passage of contrast medium through the esophagus. (Fig. 4.) The patient showed no signs of dysphagia.

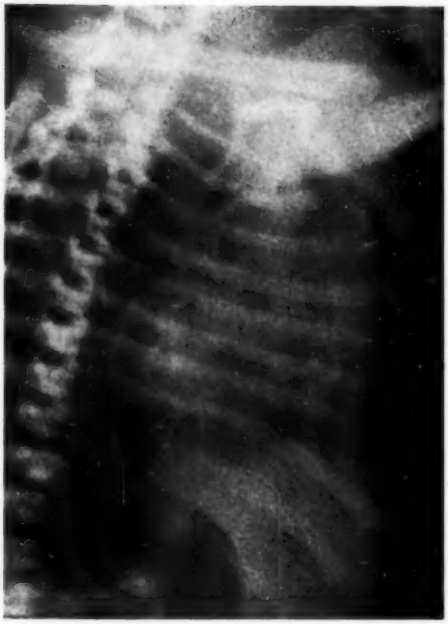

Fig. 3 a.

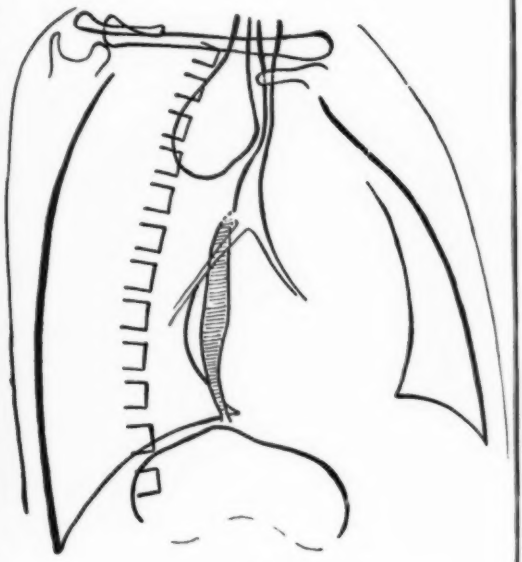

Fig. 3 b.

Fig. 3. a + b Lower segment of the esophagus filled with air which is seen to extend upwards towards the carina, crossing the right main bronchus.

Comments

The present case might well have been interpreted as type IV atresia, *i. e.* a partial atresia with dilatation of the esophagus above a stenosis with narrow passage to the lower esophageal segment. The roentgenograms, in which no contrast medium could be seen in the bronchial tree while comparatively large amounts were present in the stomach and small bowel, strongly suggested such a condition. Type IV atresia, however, is exceedingly rare. The presence of contrast medium in the stomach, therefore, may be explained by its passing from the upper blind pouch down the trachea and through the fistula to the lower portion of the esophagus without entering the bronchial tree. Operation revealed a communication between the lower portion of the trachea and the esophagus. The outer diameter of the fistula was about 0.5 cm, and the lumen was only passable for a thin sound. It is therefore probable, that changed conditions of pressure due to cough or respiration may be the cause of

Fig. 4. Five months after the operation. Slight narrowing at the site of the anastomosis, but otherwise satisfactory passage.

the contrast medium entering the stomach *in toto*. The presence of a blind pouch in the upper part of the mediastinum as demonstrated by ingestion of iodized oil as well as air and contrast medium in the gastrointestinal tract, does not provide conclusive evidence, therefore, as to whether the condition is an atresia of VOGT's type III B or a partial atresia of the type of O'BANNON. The only definite evidence of atresia of the esophagus with an upper blind pouch and with tracheo-esophageal fistula to the lower esophageal segment, is the demonstration of the air-filled passage between the trachea and the stomach.

SUMMARY

A case of congenital atresia of the esophagus of VOGT's type III B is reported. From the upper blind pouch the contrast medium has passed through the tracheobronchial fistula to the stomach without entering the bronchial tree. The differential diagnosis between VOGT's type III B and partial atresia of the type of O'BANNON is discussed.

ZUSAMMENFASSUNG

Es wird über eine kongenitale Atresie der Speiseröhre vom Vogt'schen Typus III B berichtet. Vom oberen Blindsack aus war das Kontrastmittel durch die Tracheobronchialfistel in den Magen gedrungen, ohne in den Bronchialbaum zu geraten. Die Differentialdiagnose zwischen dem Vogt'schen Typus III B und partieller Atresie vom O'Bannon'schen Typus wird besprochen.

RÉSUMÉ

Relation d'un cas d'atrésie congénitale de l'œsophage du Type III B de Vogt. Du cul de sac supérieur la substance de contraste a passé par la fistule trachéobronchique jusque dans l'estomac sans entrer dans l'arbre bronchique. Les auteurs discutent du diagnostic différentiel entre le Type III B de Vogt et l'atrésie partielle du type d'O'Bannon.

REFERENCES

1. Fuhrman, M., Dragutsky, D., Rock, G. and Grossman, L.: Aeroesophagography in Congenital Atresia of the Esophagus. Radiology 39: 100—102, July 1942.
2. Haight, C.: Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula. Reconstruction of Esophagus Continuity by Primary Anastomosis. Annals of Surgery 120: 623—652, October 1944.
3. Holt, J. F., Haight, C. and Hodges, F. J.: Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula. Radiology 47: 457—470, November 1946.
4. Ladd, W. E.: Surgical Treatment of Esophageal Fistulas. New England J. Med. 230: 625—637, May 1944.
5. Lanman, T. H.: Congenital Atresia of the Esophagus. A Study of Thirty-two Cases. Arch. Surg. 41: 1060—1083, November 1940.
6. Leven, N. L.: Congenital Atresia of the Esophagus with Tracheo-esophageal Fistula. Report of Successful Extrapleural Ligation of Fistulous Communication and Cervical Esophagostomy. Journ. Thoracic Surgery 10: 648—657, August 1941.
7. O'Bannon, R. P.: Congenital Partial Atresia of the Esophagus Associated with Congenital Diverticulum of the Esophagus. Radiology 47: 471—477, November 1946.
8. Sanderud, A.: Ösofagusatresi. Den Norske Lægefor. Tidsskr. 16: 413—414, 1948.
9. Selander, E.: Röntgenbefunde bei congenitaler Oseophagus-Atresie. Acta Radiol. 22: 802—807, 1941.
10. Solis-Cohen, L. and Levin, S.: Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula. Am. J. Dis. Child. 51: 1119—1125, May 1936.
11. Vogt, E. C.: Congenital Esophageal Atresia. Am. J. Roentg. 22: 463—465, November 1929.

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A ROD-SHAPED GALL STONE[1]

Case report

by

Rolf Köhler

Gall stones are very common, as is well-known. In some postmortem materials the incidence given is 5 to 10 per cent. They are generally multiple, and in that case faceted and of moderate size. Solitary stones occur as well, but they are globular as a rule.

A patient with a rod-shaped gall stone will now be described as its uncommon shape, and probably unique origination deserve attention.

A woman, aged thirty-nine, was given a blow in the right side of the abdomen, somewhat above the navel, in October 1944. She collapsed and lay unconscious for a while.

Some time later she had pain in the chest and below the right costal arch. They appeared with intervals of one week to one month and especially after she had been working in a stooping position. The pain lasted for half an hour to half a day.

The patient was sent to the Medical Policlinic for thorough examination as cholelithiasis was suspected. Ewald's test meal was normal; the roentgen examination of the ventricle was 0. On March 10 and 29, 1949, the author performed cholecystography: Rather large gall bladder with reduced tonus in fairly medial position. Contrast density weak. Rod-shaped negative shadow forming angle of 45° with columna. After the egg meal the gall bladder contracts well, the negative shadow has now changed its direction — — —, stretching almost from one end to the other, and is practically parallel with columna.

The roentgen finding was considered a probable non-calciferous, rod-shaped gall stone, and the patient was sent to the Surgical Hospital to be operated upon.

[1] Submitted for publication Jan. 2, 1950.

Fig. 1. Fairly large gall bladder with poor contrast density within which is seen an oblique translucent area of the shape of a finger.

Fig. 2. Adequately contracted gall bladder following egg meal. Translucent area parallel with columna.

Fig. 3. Rod-shaped concrement consisting of cholesterol covering surrounding nucleus of fibrin.

Cholecystectomy (TIITINEN) was performed on April 19, 1949, and a fairly large, sac-like gall bladder was extirpated. It contained a longitudinal concrement, of the thickness of the little finger. The Path. Report revealed slight cholecystitic changes in the bladder wall. No post-operative complications occurred. On enquiry on November 11, 1949, the patient was feeling well, the pre-operative pain appeared occasionally, but in a very mild degree.

The roentgen findings were evidently correct. The concrement was cylindrical, fairly uniform in thickness, 4.4 × 1.2 cm., yellowish brown, and its surface was moderately brilliant. The concrement was formed of two entirely different components. The superficial layer, 2—3 mm. in thickness, consisted of cholesterol. The inner part, which was blackish brown in colour stretched in the shape of a homogeneous rod through the entire concrement. It was fibrous and fairly elastic. On burning it charred and gave out a pungent smell.

The inner part of the concrement was microscopically examined by Professor WALLGREN and the findings were of great interest. A meshwork of beams of various thickness, without any cell structure of the appearance of fibrin coagulum was observed.

The origination of a gall stone of this strange, longitudinal shape must be due to some special cause. Combining the available facts, the author draws the following conclusions: Owing to the abdominal trauma, the gall bladder or the lower part of the liver has been injured probably by compression against the columna. Haemorrhage has occurred, followed by clotting of blood, either in the hepatic duct or in the gall bladder. The coagulum has become moulded into a longitudinal shape, possibly due to its origination in the hepatic duct, or to being forced to conform with the shape of the lumen in the contracted gall bladder. Structural changes have finally taken place, the fibrin has remained resistive to exterior influence and has formed the nucleus of the finger-like gall stone.

Nuclei in gall stones, formed by destructed cells, detritus and bacteria are mentioned in the literature. A nucleus of this kind is considered to stimulate the formation of stones.

Agreement has so far not been reached regarding the mechanism of origination, in spite of extensive investigations of different kinds, covering long periods. Formation of stone in the gall bladder is of extremely complex character, and the present case report may serve as an illustrative example thereof.

SUMMARY

A case with a rod-shaped gall stone, the nucleus of which consists of fibrin and the covering of cholesterol, is described. The etiology in this case was probably of traumatic nature.

ZUSAMMENFASSUNG

Ein Fall mit einem stabförmigen Gallensteine, dessen Kern aus Fibrine und Schale aus Cholesterol besteht, wird beschrieben. Die Etiologie war wahrscheinlich traumatischer Natur.

RÉSUMÉ

Un cas avec un calcul biliaire en forme de bâton dont le noyau consiste en fibrine et l'écorce en cholestérole est décrit. L'étiologie était probablement de nature traumatique.

REFERENCES

CARTER, R. F., GREENE, C. H., TWISS, J. R. and R. HOTZ: Arch. Surg. 1939: 39: 691.
FELDMAN, M.: Clinical Roentgenology of the Digestive Tract. London 1948.
ÅKERLUND, Å.: Acta Radiol. 1938: 19: 23.

FROM THE RADIUM CENTRE IN COPENHAGEN, DENMARK (CHIEF: JENS NIELSEN, M. D.)

THE TREATMENT OF THYROID CARCINOMA WITH RADIOACTIVE IODINE[1, 2]

by

Sigvard Kaae and *Olaf Petersen*

Induced radioactivity was demonstrated for the first time in 1934 (22). In the same year, FERMI (6) reported the formation of radioactive isotopes of iodine. Later, a total of about 14 different isotopes of iodine have been demonstrated, with a half-life ranging from 22 seconds to 56 days (1).

In 1938 these substances were introduced in physiological studies on rabbits (19) and shortly after the substances were used in the study of the iodine metabolism in man (13). The body deals with radioactive iodine in the same way as inactive iodine, *i. e.* there is a selective accumulation in the thyroid tissue, where the concentration will be up to 10,000 times that of the blood (16). It was only logical that next their therapeutic use was contemplated, since it was expected that perhaps this might result in a sufficient radiation intensity limited to the thyroid tissue, while the concentration of the substances in other body tissues remained too slight to be able to effect any damage, at least not primarily.

HERTZ and ROBERTS (20) as well as HAMILTON and LAWRENCE (17), in 1942, reported the treatment of hyperthyroidism with radioactive iodine, and numerous subsequent authors, nearly all from America, have published reports of large series so treated (2, 12, 21, 39 and 45). In view of the good results obtained in the treatment of benign thyrotoxicosis by different methods (operation, thiouracil and kindred substances) and of the still insufficient knowledge of the possible late effects of radioactive substances, a warning has been sounded against their use except on very strict indications, *viz.* repeated recurrences of thyrotoxicosis following operation, severe, decompensated heart disease or other lesions contraindicating surgery, lacking effect of or hypersensitivity to substances of the thiouracil group (12, 44).

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The criteria are somewhat less strict in the treatment of thyroid malignancy. In the presence of inoperable thyroid carcinoma, of recurrence, or of metastases following surgical removal of thyroid carcinoma, radioactive iodine may be tried, even in rather large doses. Owing to the very poor prognosis in such cases, the possible late effects cannot influenc the indication of the treatment to the same extent.

As early as 1938, HERTZ and EVANS (19) predicted that radioactive iodine would be useful in the treatment of thyroid malignancy, but in the subsequent year HAMILTON and SOLEY (14) reported that thyroid malignant tissue was unable to concentrate but slight amounts of iodine; their report, however, was based on only one case of malignancy. More recent investigations have shown a considerable difference in the uptake of iodine in the different varieties of thyroid carcinoma. From autoradiographic studies in 19 cases of thyroid carcinoma, MARINELLI, FOOTE, HILL and HOOKER (29) found uptake in 10. Of the latter, five were so-called »benign metastasizing» goitres. The remaining five were follicular adenocarcinomas. Among the nine patients who failed to accumulate the iodine, three suffered from Hürthle cell carcinoma and the remainder from solid alveolar or more anaplastic growths. Comparing the incidence of the various histological forms of thyroid cancer with the results obtained, these workers estimated that iodine uptake might be expected in about 15 per cent. of all thyroid carcinomas. MCARTHUR and COPE (31) administered radioactive iodine to 18 patients suffering from new growths of the thyroid gland. Six of them proved to be malignant and collected from 0—25 per cent. of the concentration found in the adjacent normal thyroid tissue. In three cases, there was a measurable iodine uptake in the secondaries. SEIDLIN, OSHRY and YALOW (37) found iodine uptake in eight of 14 cases of metastasizing thyroid carcinoma. Studying 21 cases of thyroid carcinoma, RAWSON et alii (34) found iodine uptake in the primary tumour in 10 and in the secondaries in eight. The avidity for radioactive iodine was, however, very low in all cases as compared with that of normal thyroid tissue. A comparison of the iodine-collecting capacity and the histological appearance of the tumours showed that a higher histological differentiation was usually attended by a greater iodine-collecting capacity. The same relationship between iodine uptake and histological pattern has been demonstrated by FITZGERALD and FOOTE (8) in a series of 100 patients suffering from thyroid carcinoma and showing iodine uptake in 46 per cent. and, moreover, by DOBYNS and LENNON (4) who studied benign adenomas of the thyroid gland. CHAPMAN et alii (3) found that the iodine uptake in human foetuses did not set in until at a time (fourteenth week) when follicles and colloid were developed. GORBMAN (10, 11) arrived at corresponding results in the study of foetal rat thyroids.

A complete parallelism between the histological pattern and the power to collect radioactive iodine has not, however, been demonstrated by all investigators. SEIDLIN, OSHRY and YALOW (37), for instance, did not find uptake in all malignant tumours containing colloid, whereas they found acceptable amounts of radioactive iodine in highly anaplastic carcinomas.

So far, only a few workers have reported the results of treatment of thyroid carcinoma with radioactive iodine. The first attempt was made in 1942, by KESTON, BALL, FRANTZ and PALMER (26) on a patient with a history of removal of a tumour described as »malignant adenoma» from the thyroid 35 years previously. Now, she exhibited widespread metastases in the bones, but no signs of local recurrence. A metastatic deposit at the lower end of the right femur was found to collect more radioactive iodine (30 per cent.) than the thyroid gland itself (6 per cent. of the amount administered). The remaining metastases, which had previously been treated with roentgen rays, did not collect radioactive iodine, so that a treatment with actual therapeutic doses was not instituted. According to a later report from 1944 (9) all the metastases except the one at the lower end of the right femur were poorly differentiated.

In 1946, SEIDLIN, MARINELLI and OSHRY (36) published a case of thyrotoxic, metastasizing thyroid adenocarcinoma treated with radioactive iodine. Twenty years previously, the patient had undergone total thyroidectomy for a malignant tumour of the thyroid gland. Fifteen years after the operation he developed metastases in the bones, lungs, and lymph nodes as well as hyperthyroidism. In the course of two years, he received a total of 110.8 mC of I^{130} and 158 mC of I^{131}. The primary result was satisfactory; the thyrotoxicosis subsided, and apparently the growth of the metastases was arrested. The treatment was not attended by any untoward effects.

SEIDLIN, ROSSMANN, OSHRY and SIEGEL (38) have reported the results of treatment with I^{131} in 12 cases of thyroid carcinoma. Of them seven are surviving, three showing a satisfactory result and two moderate improvement, whereas two remained stationary. Among the five deceased patients, three showed transient improvement during the treatment with radioactive iodine and two, who were moribund when the treatment was instituted, failed to respond at all. This series includes the above-mentioned patient suffering from thyrotoxic carcinoma of the thyroid gland. He has now been followed up for six years. An excised metastasis in the skull showed complete necrosis without signs of viable tumour tissue. Nevertheless, the necrotic tissue from the destroyed metastasis was still able to concentrate iodine.

TRUNNEL et alii (42) observed definite clinical improvement in four out of a series of nine. This improvement consisted in a shrinkage of the tumour mass and histological evidence of cell destruction. A few toxic

effects were observed, *i. e.* hyperthyroidism in three previously euthyroid patients, amenorrhoea in three females below 41 years of age, and signs of depression of the haemopoietic activity of the bone marrow in all the patients receiving large doses of radioactive iodine.

In a certain number of cases, the iodine uptake in metastases from thyroid carcinoma may be increased by surgical removal of the entire thyroid body or destruction of the latter by means of large doses of radioactive iodine (33, 37, 38, 42). According to these workers, the interval from thyroidectomy until increased iodine uptake is demonstrable in the secondaries ranges from one to 32 months. The iodine uptake in the metastases may also be increased by administration of thyrotropic hormone (23, 37, 38, 42, 43) or by simultaneous administration of thyrotropic hormone and thiouracil (34), since it has been found that thiouracil cannot block the iodine uptake in the malignant tissue in cases of thyroid carcinoma. These findings might, therefore, indicate that the mechanism of iodine concentration in thyroid malignant tissue is different from that applying to normal thyroid tissue.

Methods of Determining of Radioactive Iodine in the Tumour Tissue

The methods employed to measure the ability of malignant tissue to accumulate iodine are as follows:

(1) Direct determination of the I^{131} activity in biopsy specimens.
(2) Histo-autoradiography.
(3) Measurements *in vivo* of the radioactivity with the Geiger-Müller counter.
(4) Determination of the activity of the I^{131} excreted in the urine.

Re (1). Direct determination of the I^{131} content in biopsies or operation specimens may be done by destroying the tissue in 2n NaOH and determining the activity of the resulting solution by means of the Geiger-Müller counter. The activity is compared with a standard solution of I^{131} (7, 34). This method gives the I^{131} content per g. of tissue, and if the size of the tumour is known, the approximate radiation intensity may be computed (30).

Re (2). Histoautoradiography illustrates the distribution of the radioactive substance in relation to the histological pattern of the tissue. One or more days before operation or biopsy, a suitable amount of I^{131} is administered, and from the removed tissue specimens, histological sections are prepared in the usual way. The most simple method is the one of superimposing a sensitive roentgen film on the unstained section and developing the film after the lapse of varying intervals. Thereupon, the histological specimen is prepared in the usual manner. This affords

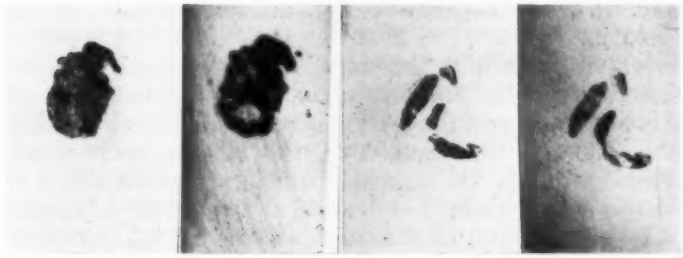

Fig. 1. Fig. 2.

Fig. 1. Histo-autoradiogram using a roentgen film. Operation specimen from a primary thyroid carcinoma. Normal B. M. R. On the left the stained histological section, on the right the histo-autoradiogram. The lighter parts of the blackening on the film represent cell-poor areas. Satisfactory iodine uptake all over the malignant tissue.

Fig. 2. Case 50997. Histo-autoradiogram using a roentgen film. Trephine biopsy from a pelvic metastasis eight weeks after complete thyroidectomy followed by thyrotropic hormone therapy. On the left the stained histological section, on the right the histo-autoradiogram. Irregular blackening, indicating satisfactory iodine uptake by the neoplastic tissue in some places, hardly any in others.

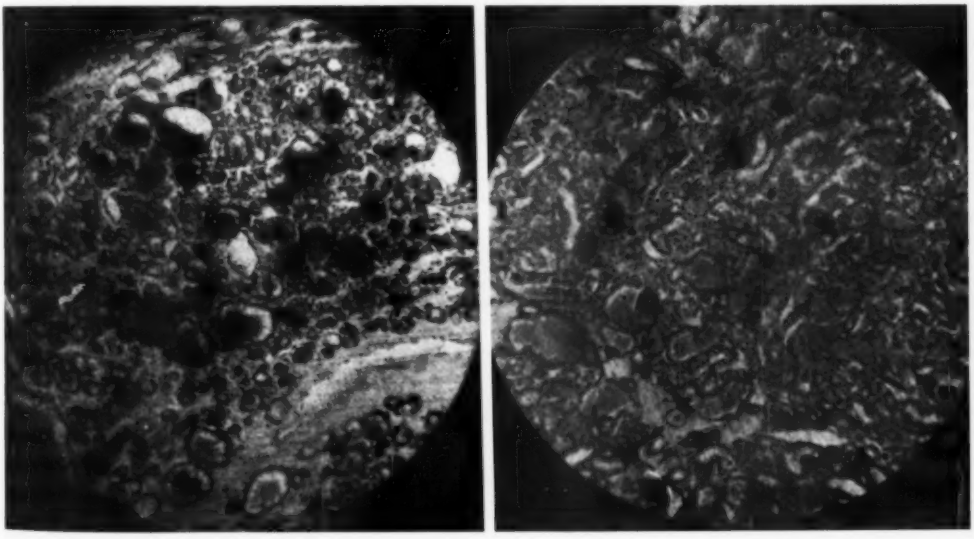

Fig. 3. Fig. 4.

Fig. 3. Histo-autoradiogram obtained by superimposing the histological section on a lantern-slide plate. The same preparation as Fig. 1. Satisfactory, fairly evenly distributed iodine uptake in the follicles.

Fig. 4. Histo-autoradiogram obtained by superimposing the histological section on a lantern-slide plate. Same preparation as Fig. 2. Irregular distribution of the small amount of iodine accumulated in the follicles.

a rough picture of the distribution of radioactive substance in the section (Figs. 1 and 2).

To obtain finer details, the unstained histological section may be placed directly on a lantern-slide plate. After varying exposure times, the plate is developed and the section is prepared directly on the lantern-slide plate. Through the microscope, the blackening in the emulsion will be visible through the stained histological section (Figs. 3 and 4). Using a lantern-slide plate, however, it is impossible to avoid a slight staining of the emulsion, as the section is passed through the various staining solutions. This can be avoided by using stripping films. For this technique and the further details of histo-autoradiography, the reader is referred to a very able monograph by YAGODA (46).

Re (3). Measurements *in vivo* by the Geiger-Müller counter in order to ascertain the approximate I^{131} content in the tissues are subject to considerable sources of error: Absorption and scatter of the rays in the tissues, radioactivity in other parts of the body, the geometrical relation of the apparatus to the active tissues, the stability of the counting tube and scaler etc. (5, 15, 25, 28, 32, 40). In order to convert the number of counts measured per minute to absolute values, microcuries, or per cent. of the amount received, a comparison with a standard solution is necessary. At the present time, however, such values must be called extremely inaccurate, and the writers have, therefore, restricted themselves to stating relative values. In that case, daily measurements may afford valuable data as to the variations in the I^{131} content of the tissue, forming the basis of activity curves. If the absolute content of I^{131} in a biopsy specimen is determined by the method described above, the absolute values, microcuries per g. of tissue, are stated in a point on the curve. From this point, the other points of the curve may be converted into absolute standards, and the intensity of radiation may be calculated.

In order to shield from radiation from other parts of the body than the site directly under the counting tube, the writers used a »telescope device», consisting of a lead tube, 42 cm. in length and with a wall thickness of 6 mm.

Re (4). The urine analyses may be performed on the lines recommended by KEATING and co-workers (24).

Writers' Investigations

The treatment of thyroid carcinoma with radioactive iodine was commenced at the Radium Centre in Copenhagen in January 1948, but since the shipments of I^{131} from the Oak Ridge National Laboratory, U. S. A., were not regular until September 1948, the treatment was not systematized until that time.

This treatment is used only in cases of inoperable thyroid carcinoma or of recurrences and metastases following previous operation for thyroid carcinoma. It has, however, been used in a few cases of benign thyrotoxicosis who had undergone repeated operations and been treated with substances of the thiouracil group without effect.

All the patients have first received a tracer dose of I^{131}, usually 100—500 microcuries. By studying the urinary excretion of iodine during the first four days, the amount of iodine retained in the body was ascertained. This study is of particular interest in patients who have undergone complete thyroidectomy or those in whom the function of normal thyroid tissue has been completely arrested by earlier administration of a large amount of I^{131}. In such cases, it must be presumed that the retained amount of I^{131} will be accumulated almost exclusively in the thyroid malignant tissue (40). It has, furthermore, been attempted to localize the iodine uptake by means of the Geiger-Müller counter, at the outset with daily measurements. In an endeavour to eliminate the radiation from the thyroid gland in cases where normal thyroid tissue remains, the counting tube was shielded with a lead tube and the iodine uptake in the metastases measured at a distance of 36 cm.

In nearly all cases biopsy specimens could be removed, usually with a rotating trephine, from the thyroid malignant tissue, be its site in the neck, spine, or pelvis. This method easily yields up to $^1/_2$ g. of tissue. Moreover, histo-autoradiographic studies have afforded a rough estimate of iodine uptake, if any, and it has been possible to observe the distribution of the radioactive iodine in the section. In addition the I^{131} content per gramme of tissue was determined directly as mentioned above. In cases submitted to complete thyroidectomy, it is possible, by a comparison of the iodine concentration in the tissue and the retained amount of iodine, to compute the approximate weight of the tumour tissue and on this basis estimate the intensity of the radiation in rep in the tumour. When compared with the daily measurements with the Geiger-Müller counter *in vivo* over the tumour, these values afford a basis for a calculation of the daily radiation intensity in the tumour, so long as it is of approximately the same size.

Although these calculations are no doubt beset with fairly great inaccuracy, especially because of the heterogeneous distribution of the radioactive iodine in the tumour, it is possible to obtain evidence as to whether the doses given are actually of therapeutic value.

Among patients suffering from carcinoma of the thyroid gland, a total of 19 were examined from the point of view of treatment with radioactive iodine. Of them, six were so ill that regular treatment was not even attempted, and most of them died a few weeks later. One patient did not receive treatment, since the chances of iodine uptake in the

tumour tissue were considered minimal and the patient wanted to get back to her home in the Faroe Islands.

Three patients were referred to the Radium Centre after having undergone unradical operations because of invasion into the surrounding tissues. None of these cases exhibited palpable tumours or demonstrable remote metastases, so that it was impossible to ascertain, whether the neoplastic tissue did collect iodine. All three are alive symptom-free and are still under observation.

The series includes three cases of thyrotoxic carcinoma of the thyroid gland. One of the patients, a 54-year-old male, suffering from a large inoperable, intrathoracic, undoubtedly malignant goitre, had previously received iodine and methyl thiouracil treatment which resulted in transient improvement. On admission, the basal metabolic rate was + 30 per cent. In this case, only the thyrotoxicosis was treated. It was endeavoured to bring the metabolic rate down to a normal level by means of I^{131}, but he was treated so recently, that the late results cannot be reported.

The case histories of the other two patients suffering from thyrotoxic carcinoma of the thyroid gland will be reported in some detail:

Case rec. No. 49578. An unmarried female, aged 32, admitted to the Radium Centre on Sept. 23, 1948. She had undergone subtotal operation for a thyrotoxic goitre at the University Hospital 15 years previously. Microscopical examination revealed a poorly differentiated carcinoma without follicles or colloid substance. She had received postoperative roentgen therapy.

Since then, the patient had not been well, exhibiting thyrotoxic symptoms and being unable to look after her work except in periods. In 1942 she was found to exhibit pulmonary changes which, according to the course of her condition, were interpreted as metastases. In 1944, enlarged lymph nodes were removed from the left axilla. One of these nodes was found to contain a carcinomatous metastasis the histological appearance of which conformed to a thyroid carcinoma, showing small glands with traces of colloid. Since no other primary tumour has been diagnosed, the phenomenon is no doubt interpretable as a metastasis from the thyroid carcinoma.

The patient was treated with roentgen-ray irradiation of the neck, with diiodotyrosine, digitalis, and quinidine as well as sedatives without much effect on the thyrotoxic symptoms. During the past three years she had been receiving methyl thiouracil in daily doses varying, according to her condition, up to 60 cg. The B. M. R. which, at any rate since 1942, had been greatly enhanced, fluctuating from + 27 to + 65 per cent., was now brought down to a normal level. It did not, however, remain normal, being now too low, now too high with corresponding symptoms, so that during the last couple of years the patient had been unable to look after her work and could hardly even help her mother with the domestic duties. On admission to the Radium Centre on Sept. 23, 1948 the patient was in a state of pronounced thyrotoxicosis with a B. M. R. of + 30 per cent. She was emaciated, nervous, tearful, and restless. At the site of the thyroid gland, a swelling, 2 × 2 × 2 cm., was palpable to the right of the trachea. Numerous, small, hard, calcified lymph nodes were found on both sides of the neck and one hard lymph node, about 1 × 1 cm., in the left supraclavicular region.

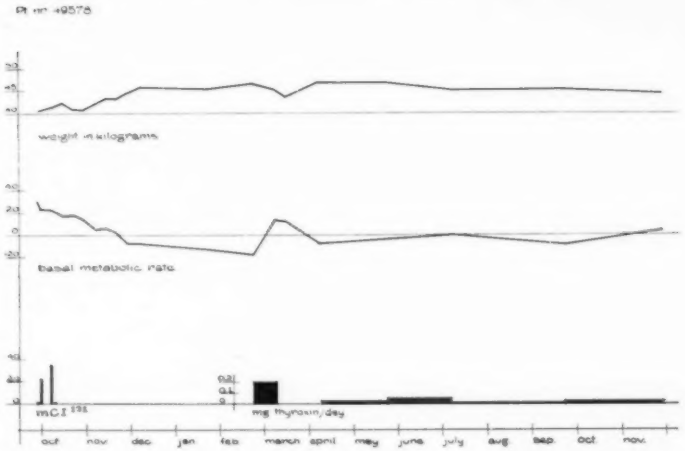

Fig. 5. Case 49578. Thyrotoxic carcinoma of the thyroid gland with remote metastases treated with I^{131}.

Roentgen examination of the lungs showed an intense, patchy pattern on both sides, showing numerous small calcified spots which were also found in the liver. The changes were practically unchanged from the findings seven years previously. Following administration of a tracer dose of I^{131}, iodine uptake was demonstrated in the swelling to the right of the trachea, and microscopical examination of a biopsy specimen showed thyroid tissue, in places with small papillae in the lumen, but with no histological signs of malignancy. The hard lymph nodes on the sides of the neck failed to collect iodine, and microscopical examination of a couple of excised lymph nodes showed bony tissue with clusters of epithelial cells, resembling the cells of the thyroid body, so that they are presumably interpretable as ossified metastases from the thyroid carcinoma.

The Geiger-Müller counter failed to demonstrate a definite uptake of iodine in the pulmonary metastases. Aspiration biopsy from the right lung showed a solid clump of epithelial cells with extremely varying nuclei which might fit the picture of a metastasis. The patient was now treated with I^{131}, receiving from Sept. 25 to Nov. 11, 1948 a total of 60 mC (Fig. 5). The metabolic rate fell steadily, and the condition improved rapidly. A little more than a month after the commencement of treatment, the patient, who had been tied to her bed and unable to sit up without violent palpitations and a vigorous pulsation on the neck, could move about without discomfort. Her appetite improved, and she gained weight. (The appetite was, however, somewhat affected by a pronounced megacolon.) In the course of six weeks, the B. M. R. fell to normal values, and it went on falling, so that five months after the commencement of treatment it was — 18 per cent. At the same time, symptoms of myxoedema appeared, but it proved possible to retain the B. M. R. on a normal level on thyroidin. The patient is now feeling better than she has been for years, and she has been able to undertake light work. Now, 15 months after the commencement of treatment, the condition is completely satisfactory and there are no signs of progression of the metastases. Following administration of a tracer dose of I^{131}, 18 per cent. were retained, indicating the presence of tumour tissue producing thyroid hormone.

The treatment of a 32-year-old female suffering from metastasizing thyrotoxic carcinoma of the thyroid gland with radioactive iodine gave a satisfactory result, lasting to this day, 15 months after the commencement of treatment.

Case rec. 50997. A female, aged 47, who was admitted to the Radium Centre in January, 1949.

History of syphilis in 1920.

Two years ago, she had had »rheumatic» pain in the left hip, radiating into the left lower limb. She received physical treatment without effect. In October 1948 she was admitted to the Bispebjerg Hospital, where a large tumour was found in the left pelvis, arising, apparently, from the area around the floor of the acetabulum. She was treated with iodine in large doses (as it was suspected that the tumour was of gummatous nature) and later with roentgen, 1,650 r. Since the treatment proved ineffective, the patient was transferred to the Radium Centre on Jan. 26, 1949.

There, a tense, soft, cystic, apparently pulsating tumour was found on the inside of the left pelvic wall, adhering firmly to the bone. Roentgen examination showed a soft-tissue tumour, 11 × 5 cm., and a destruction, measuring 4 × 9 cm., of the bodies of the ilium, ischium, and pubic bone. In the right lobe of the thyroid body, an adenoma-like tumour, the size of a pigeon's egg, was palpable.

A biopsy specimen from the pelvic tumour showed a pattern like regular thyroid tissue with numerous large and small, highly differentiated follicles containing colloid. Following administration of I^{131}, 600 microcuries, the Geiger-Müller counter failed to register iodine uptake in the pelvic metastasis. On March 25, 1949, therefore, total thyroidectomy was done in order to increase the iodine uptake of the secondary tumour, if possible. In the basal area of the right lobe there was a whitish tumour, 22 × 22 × 22 mm., apparently encapsuled, but showing invasion in one site inferiorly. Histo-autoradiography showed only slight uptake of iodine in the tumour, whereas in the normal thyroid tissue the uptake was satisfactory, despite the almost uniform histological appearance of the two.

From April 4—29, 1949, she received a daily dose of thyrotropic hormone (Ambinon »Organon»), 1 ml., and from April 26 to July 14, 1949, I^{131}, a total of 576 mC by mouth in doses of 6.43 to 190.4 mC. The intervals between the doses ranged from 10 to 21 days.

After the operation, the metabolic rate fell steadily from March 21 (+ 30) until July 13, when it was — 18 per cent.

The serum cholesterol rose evenly from March 4: 173 mg. per cent. to May 28, when it was 342 mg. per cent.

The white blood cell level, controlled by weekly counts, remained comparatively unaffected at 4,000—5,000 per c. mm. at the outset, but in the middle of July it dropped to 2,840 per c. mm. Two months after the iodine medication was stopped, the W. B. C. again reached normal values. A punctate of sternal bone marrow on Aug. 30, 1949 showed slight hypoplasia and a shift to the left in the blood picture, indicating initial radiation damage of the bone marrow. Therefore, the treatment with radioactive iodine was not resumed.

During the first few postoperative months, the fall in the B. M. R. was accompanied by unmistakable subjective improvement. Later on, mild myxoedematous symptoms set in, but since the patient feels better without thyroidin than on even small doses, and since another course of I^{131} has been planned, thyroidin is not being administered for the present. The pains in the left pelvis radiating down into the left lower limb are on the whole unchanged, at any rate not improved. Neither digital palpation nor roentgen examination have revealed a shrinkage of the soft-tissue tumour in the left pelvis. It has

remained unchanged, and by the end of November 1949, the floor of the acetabulum was completely destroyed, and there was subluxation of the femoral head. There is no doubt that the neoplastic tissue extended as far as the acetabulum before the treatment was instituted.

After a large single dose of I^{131} (190 mC) had been given on June 23, marked tender swelling of both submaxillary salivary glands was noted on the subsequent day. The swelling subsided spontaneously in the course of five days, leaving some firmness. According to the studies of the urinary excretion during the first four days, about 20 per cent. of the entire amount had been retained. A trephine biopsy from the pelvic metastasis following a large dose of I^{131} yielded 320 mg. of tumour tissue (Fig. 2 and 4). The I^{131} content was determined, and the weight of the tumour tissue was calculated as about 400 g. By means of Marinelli's formulae the daily dose in the tumour tissue in rep could be determined. By also carrying out daily measurements with the Geiger-Müller counter, it was possible to calculate the approximate daily dose in the tumour in rep during the entire period while radio-iodine was being administered.

The calculated dose in the central area of the tumour was about 7,000 rep in the course of about nine weeks. Of this dose, about 5,000 rep were received in the course of 26 days. The exact dose required to cure a thyroid carcinoma, if possible, is not known. By fractionated roentgen-ray treatment, resulting in a tumour dose of about 4,800 r, HARE (18) obtained only a clinical arrest of the cancer. A highly differentiated thyroid carcinoma, like the one in question, no doubt requires a higher dose than a skin carcinoma. According to STRANDQVIST (41), a skin carcinoma requires 5,800 r in the course of 26 days. It must, however, be borne in mind that roentgen ray doses in r are hardly directly comparable with predominantly beta radiation in rep in the tumour tissue, even though the slight dose in rep in the peripheral area, particularly in the outermost mm. of the tumour, is disregarded. I^{131} results in far less radiation of the stroma around the tumour (the »tumour bed») than roentgen-ray radiation. This appears to be of decisive significance to the effect of roentgen-ray radiation. The necessary dose in rep from a beta-producing isotope must, therefore, be presumed to be higher still.

In this case, the reaction on the part of the bone marrow prevented us from obtaining a higher tumour dose which would have been obtained if the tumour had collected a higher percentage of the I^{131} administered, *e. g.* 50 per cent. instead of about 20 per cent. It would no doubt have been preferable to defer the treatment with large doses of radioactive iodine until thyrotropic hormone had been given for a little longer.

Owing to the swelling of the submaxillary salivary glands which resulted from the administration of 190 mC of I^{131}, the concentration in the saliva was determined for the first four days after the administration of the next dose of I^{131}. It was found to range from 435 to 235 per cent. of the concentration in the urine on the same day. Following administration of a tracer dose of I^{131}, SCHIFF et alii (35) found considerable concentration of the substance in the gastric juice and saliva.

Similar studies in two other cases showed a concentration of I^{131} in the saliva of 105 to 140 per cent. that of the urine.

In addition, two females, aged 79 and 84, with thyrotoxic goitre (B. M. R. + 33 and + 32 per cent.) have been treated. Histological examinations failed to give any evidence of malignancy, and there were no metastases, but clinically they are suspected of malignancy. Because of the patients' age, they were given only about 5 mC of I^{131} in an endeavour to overcome the thyrotoxicosis, but as yet the follow-up period is too brief.

Among the remaining four euthyroid patients suffering from carcinoma of the thyroid body, two were submitted to total thyroidectomy with a view to later I^{131} therapy.

One of them, a 69-year-old female, had metastases in the dorso-lumbar vertebrae which had previously been treated with roentgen rays. She was rather ill and bedridden and died on the fourth postoperative day from pulmonary complications. Microscopic examination of the tumour showed a normal thyroid tissue with small follicles. There was only a slight uptake of radio-iodine.

The second patient was a 50-year-old female with lumbo-sacral metastases. Biopsy from this site showed thyroid tissue of normal appearance, but following administration of a tracer dose of I^{131}, the Geiger-Müller counter failed to register iodine uptake in the metastasis. Recently, total thyroidectomy was done following administration of a tracer dose of I^{131}. The concentration of I^{131} in the primary tumour, which weighed 2.5 g., was only 1.8 per cent. of the concentration in the normal thyroid tissue in spite of only a very slight histological difference. When the secondaries begin to collect large amounts of iodine, perhaps following administration of thyrotropic hormone, I^{131} will be started in therapeutic doses.

The third patient was a man, aged 64, suffering from a large inoperable left-sided thyroid carcinoma, determined histologically as a solid thyroid carcinoma. No uptake was demonstrable in the tumour after the administration of a tracer dose of I^{131}. In order to arrest the function of the normal thyroid tissue, he has been given I^{131}, 40 millicuries, and provided that his condition allows it, I^{131} therapy will be attempted later.

The fourth euthyroid patient with thyroid carcinoma treated with I^{131} has been followed up somewhat longer and will be reported below:

Case rec. 47580. Female, aged 67, referred to the Radium Centre in March 1948. In January 1944 a large, hard nodule in the right lobe of the thyroid had been removed at the Finsen Institute, Department of Surgery. Micr. diagnosis: Cystic, colloid goitre, adenoma of the thyroid gland. Before the operation, the B. M. R. was normal.

The patient remained completely symptom free until March 1947, when she began

to suffer from increasing respiratory distress, attacks of cough and periodical expectoration of fresh blood, often in considerable amounts. The symptoms progressed until March 1948, when the patient was re-admitted to the Finsen Institute, Department of Otology. Bronchoscopy showed: 1.5—2 cm. below the vocal cords, there is a flat, irregular prominence from the right aspect of the trachea. A biopsy specimen showed: Groups of poorly differentiated epithelial cells with densely packed hyperchromatic nuclei. Furthermore, in places adenoma-like tissue with small colloid-filled lumina.

In March 1948, the patient was transferred to the Radium Centre. Clinical examination showed a firm, rather diffuse mass, 5 × 3 cm., at the site of the right lobe of the thyroid gland. Roentgen-ray therapy was instituted at once, four fields on the anterior aspect of the neck, a total of 5,920 r in the course of 36 days. The tumour shrunk somewhat, but at the end of the treatment, a mass as large as a walnut remained, and minor haemoptyses persisted. In June 1948, a tracer dose of I^{131} was administered, and measurements with the Geiger-Müller counter showed a certain uptake.

From July 7 to August 7, 1949, she received a total of 241.5 mC of I^{131} in doses of from 7.7 to 79.6 mC at intervals of from three weeks to three months. The treatment was attended with considerable subjective improvement, particularly at the outset. The haemorrhages were arrested and have not recurred. Bronchoscopy, which in March 1949 had shown tumour tissue immediately below the glottis posteriorly on the right lateral wall of the trachea, extending 2—3 cm. down, showed no tumour tissue in October, 1949. At the site of the earlier tumour there was now a small notch without ulceration. A trephine biopsy from the tumour on the right neck in August 1949 showed fibrosis and resorptive processes, but tumour tissue was not demonstrated.

Examination in December 1949 revealed a slight, diffuse, fibroid firmness to the right of the trachea, but no other abnormalities. The treatment with radicactive iodine did not at any time result in perceptible ill effects, except for the myxoedema which was treated with thyroxin.

In this case of recurrence following surgical removal of a thyroid carcinoma invading the trachea, the treatment with I^{131} resulted not only in subjective improvement, but also in complete disappearance of the tumour tissue in the trachea.

Conclusion

At the present time, the experience from the treatment of thyroid carcinoma with radioactive iodine is so limited and the results so uncertain that all operable cases should be operated, and the treatment with radioactive iodine should be reserved for the inoperable cases. The results appear to be most satisfactory in thyrotoxic carcinoma of the thyroid gland in which cases the iodine uptake in the malignant tissue is more satisfactory. Thyrotoxic thyroid carcinoma is usually of slow growth, and previously the patients usually succumbed to the thyrotoxicosis. Now, the latter can easily be overcome by radioiodine. Its power to inhibit the growth of the thyroid carcinoma proper has not yet been definitely ascertained. Studies following administration of tracer doses of iodine indicate the continued presence of tumour tissue producing thyroid hormone as in the case reported above. A thyroid carcinoma with no

effect in the metabolism rate usually collects so little iodine that primarily the function of the normal thyroid tissue must be arrested, either by surgical removal of the entire thyroid gland or by administration of a large dose of radioactive iodine (a minimum of 40 mC of I^{131}). One must then await the time when the malignant tissue begins to take up more iodine, a process which may be precipitated by administration of thyrotropic hormone. It is not until then that the concentration of radioactive iodine in the thyroid malignant tissue can be high enough to afford a possibility of obtaining therapeutic doses. As yet, it is difficult to say how often such attempts will be successful. Among the present series, we succeeded in one case.

No conformity was found between the histological pattern and the uptake of radioactive iodine. In three cases of benign metastasizing thyroid adenoma, for instance, slight or no iodine uptake was found in the primary tumour and the metastases. Following complete thyroidectomy, however, the metastases were found to collect fairly large amounts of iodine in the two cases. (One of the patients died after the operation.) In one case of thyrotoxic thyroid carcinoma, in which the malignant tissue must have produced thyroid hormone, the histologic picture was one of a poorly differentiated carcinoma without follicles or colloid substance. The histological appearance, therefore, does not appear to help to decide in which cases treatment with radioiodine should be attempted.

Despite previous roentgen therapy of metastases from thyroid carcinoma, a quite considerable iodine uptake was obtained in two cases, resulting in one in complete disappearance of visible tumour invasion in the trachea. Previous roentgen therapy should, therefore, not contraindicate attempts at treatment with radioactive iodine.

SUMMARY

After reviewing the literature, the writers report their own results. Their series includes a case of thyrotoxic carcinoma of the thyroid gland with remote metastases, treated with I^{131} with a satisfactory result lasting to this day, 17 months after. In another case of recurrence following operation for a thyroid carcinoma, the tumour had invaded the trachea. The basal metabolic rate was normal. The malignant tissue in the trachea yielded completely to treatment with I^{131}.

In addition to the inevitable myxoedema, which is treated with thyroidin, the complications consisted in a depression of the haemopoietic activity of the bone marrow in one case and in transient swelling of the submaxillary salivary glands in the same (radioactive iodine is excreted in rather high concentration in the saliva).

No conformity was found between the histological pattern and the uptake of radioactive iodine in the thyroid malignant tissue. Therefore, it could not be decided histologically which cases were likely to respond to treatment with radioactive iodine. Previous roentgen therapy did not prevent concentration, even of considerable amounts, of radioactive iodine in the tumour tissue.

ZUSAMMENFASSUNG

Nach einem Überblick über das Schrifttum bringen Verff. ihre eigenen Ergebnisse. Ihr Material umfasst u. a. einen Fall von thyreotoxischem Krebs der Schilddrüse mit Fernemetastasen der mit I^{131} behandelt wurde, und zwar mit gutem Erfolg, der noch heute, nach 17 Monaten, andauert. Bei einem anderen Falle von Rückfall nach Operation wegen eines Schilddrüsenkrebses hatte der Tumor die Luftröhre angegriffen. Der Grundumsatz war normal. Das maligne Gewebe in der Luftröhre wurde durch Behandlung mit I^{131} vollständig beseitigt.

Ausser in dem unvermeidlichen Myxödem, das mit Thyroidin behandelt wird, bestanden die Komplikationen bei einem Falle in einer Verminderung der blutbildenden Tätigkeit des Knochenmarks und bei demselben Falle in vorübergehender Schwellung der submaxillaren Speicheldrüsen (radioaktives Jod wird in ziemlich starker Konzentration mit dem Speichel ausgeschieden).

Zwischen dem histologischen Bilde und der Aufnahme von radioaktivem Jod des malignen Schilddrüsengewebes wurde keine Übereinstimmung gefunden. Es liess sich also histologisch nicht entscheiden, welche Fälle wahrscheinlich auf Behandlung mit radioaktivem Jod ansprechen würden. Voraufgehende Röntgenbehandlung verhinderte nicht eine Anhäufung von selbst bedeutenden Mengen von radioaktivem Jod im Tumorgewebe.

RÉSUMÉ

Après une revue de la littérature les auteurs rapportent leurs propres résultats. Dans leur série il y a un cas de cancer thyréotoxique du corps thyroïde avec des métastases à distance, qui fut traité par l'I^{131} avec un effet satisfaisant, se maintenant jusqu'à ce jour, 17 mois après. Dans un autre cas de récidive à la suite de l'opération d'un cancer de la thyroïde, la tumeur avait envahi la trachée. Le métabolisme basal était normal. Le tissu de nature maligne au niveau de la trachée disparut complètement par le traitement à l'I^{131}.

En plus du myxœdème inévitable, qu'on traite par la thyroïdine, les complications ont consisté en une inhibition de l'activité hématopoïétique de la moelle osseuse dans un cas, et chez le même sujet en une tuméfaction passagère des glandes salivaires sous-maxillaires (l'iode radioactif est excrété en concentration plutôt élevée avec la salive).

On n'a pas trouvé de concordance entre le type histologique du tissu thyroïde malin et sa capacité d'absorption de l'iode radioactif. Aussi ne faut-il pas se baser sur l'histologie pour choisir les doses ayant chance d'obtenir une réponse favorable, dans le traitement par l'iode radioactif. La radiothérapie anterieure n'a pas empêché la concentration, même en quantités considérables, de l'iode radioactif dans le tissu néoplasique.

LITERATURE

1. Chaikoff, I. L. and Taurog, A.: Application of radioactive iodine in studies in iodine metabolism and thyroid function. The use of isotopes in biology and medicine, p. 292. The University of Wisconsin press, 1948.
2. Chapman, E. M. and Evans, R. D.: The treatment of hyperthyroidism with radioactive iodine. J. A. M. A. 131: 86—92, 1946.
3. Chapman, E. M., Corner, G. W., Robinson, D. and Evans, R. D.: The collection of radioactive iodine by the human fetal thyroid. J. Clin. Endocrinol. 8: 717—720, 1948.

4. Dobyns, B. M. and Lennon, B.: A study of histopathology and physiologic function of thyroid tumors using radioiodine and radioautography. J. Clin. Endocrinol. 8: 732—748, 1948.
5. Dobyns, B. M., Skanse, B. N. and Maloof, F.: A method for the preoperative estimation of function in thyroid tumors: its significance in diagnosis and treatment. J. Clin. Endocrinol. 9: 1171—1189, 1949.
6. Fermi, E.: Radioactivity induced by neutron bombardment. Nature, London, 133: 757, 1934.
7. Findlay, D. and Leblond, C. P.: Partial destruction of rat thyroid by large doses of radio-iodine. Am. J. Roentgen. 59: 387—395, 1948.
8. Fitzgerald, P. J. and Foote, F. W.: The function of various types of thyroid carcinoma as revealed by the radio-autographic determination of radioactive iodine (I^{131}). J. Clin. Endocrinol. 9: 1153—1170, 1949.
9. Frantz, V. K., Ball, R. P., Keston, A. S. and Palmer, W. W.: Thyroid Carcinoma with metastases: studied with radioactive iodine. Ann. Surg. 119: 668—689, 1944.
10. Gorbman, A. and Evans, H. M.: Time of beginning of function in the thyroid glands of fetals rats. Anat. Rec. 81 (Suppl.): 95—96, 1941.
11. Gorbman, A. and Evans, H. M.: Beginning of function in the thyroid of the fetal rat. Endocrinology 32: 113—115, 1943.
12. Haines, S. F., Keating, F. R., Power, M. H., Williams, M. M. D. and Kelsey, M. P.: The use of radio iodine in the treatment of exophthalmic goiter. J. Clin. Endocrinol. 8: 813—825, 1948.
13. Hamilton, J. G.: The rates of absorption of the radioactive isotopes of sodium, potassium, chlorine, bromine and iodine in normal human subjects. Am. J. Physiol. 124: 667—678, 1938.
14. Hamilton, J. G. and Soley, M. H.: Studies in iodine metabolism by the use of a new radioactive isotope of iodine. Am. J. Physiol. 127: 557—572, 1939.
15. Hamilton, J. G. and Soley, M. H.: Studies in iodine metabolism of the thyroid gland in situ by the use of radio-iodine in normal subjects and in patients with various types of goiter. Am. J. Physiol. 131: 135—143, 1940.
16. Hamilton, J. G.: The use of radioactive tracers in biology and medicine. Radiology, 39: 541—572, 1942.
17. Hamilton, J. G. and Lawrence, J. H.: Recent clinical development in therapeutic application of radio-phosphorus and radio-iodine. J. Clin. Invest. 21: 624, 1942.
18. Hare, H. F.: Radiation treatment of carcinoma of the thyroid. Am. J. Roentgen. 46: 451—453, 1941.
19. Hertz, S., Roberts, A. and Evans, R. D.: Radioactive iodine as an indicator in the study of thyroid physiology. Proc. Soc. Exper. Biol. and Med. 38: 510—513, 1938.
20. Hertz, S. and Roberts, A.: Application of radio-iodine in therapy of Graves' disease. J. Clin. Invest. 21: 624, 1942.
21. Hertz, S. and Roberts, A.: Radioactive iodine in thyroid physiology VII. The use of radioactive iodine therapy in hyperthyroidism. J. A. M. A. 131: 81—86, 1946.
22. Joliot, F. and Curie, I.: Artificial production of a new kind of radio-element. Nature, London, 133: 201—202, 1934.
23. Keating, F. R., Rawson, R. W., Peacock, W. and Evans, R. D.: The collection and loss of radioactive iodine compared with the anatomic changes induced in the thyroid of the chick by the injection of thyrotropic hormone. Endocrinology, 36: 137—148, 1945.

24. KEATING F. R., POWER, M. H., BERKSON, J. and HAINES, S. F.: The urinary excretion of radio-iodine in various thyroid states. J. Clin. Invest. 26: 1128—1151. 1947.
25. KEATING, R. F., WANG, J. C., LUELLEN, T. J., WILLIAMS, M. M. D., POWER, M. H. and MCCONAHEY, W. M.: The measurement of the iodine-accumulating function of the human thyroid gland. J. Clin. Invest. 28: 217—227, 1949.
26. KESTON, A. S., BALL, R. P., FRANTZ, V. K. and PALMER, W. W.: Storage of radioactive iodine in a metastasis from thyroid carcinoma. Science, 95: 362—363, 1942.
27. LEITER, L., SEIDLIN, S. M., MARINELLI, L. D. and BAUMAN, E. J.: Adenocarcinoma of the thyroid with hyperthyroidism and functional metastases. J. Clin. Endocrinol. 6: 247—261, 1946.
28. LUELLEN, T. J., KEATING, F. R., WILLIAMS, M. M. D., BERKSON, J., POWER, M. H. and MCCONAHEY, W. M.: Relative measurement in vivo of accumulation of radio-iodine by the human thyroid gland: comparison with radioactivity in peripheral tissues. J. Clin. Invest. 28: 207—216, 1949.
29. MARINELLI, L. D., FOOTE, F. W., HILL, F. R., HOOKER, A. F.: Retention of radioactive iodine in thyroid carcinomas. Histopathologic and radio-autographic studies. Am. J. Roentgen. 58: 17—32, 1947.
30. MARINELLI, L. D., QUIMBY, E. and HINE, G. J.: Dosage determination with radioactive isotopes. II. Practical considerations in therapy and protection. Am. J. Roentgen, 59: 260—280, 1948.
31. MCARTHUR, J. W. and COPE, O.: The functional capacity of thyroid tumors as judged by radioactive iodine uptake. J. Clin. Invest. 25: 929, 1946.
32. QUIMBY, E. H. and MCCUNE, D. J.: Uptake of radioactive iodine by normal and disordered thyroid gland in children, a preliminary report. Radiology, 49: 201—205, 1947.
33. RAWSON, R. W., MARINELLI, L. D., SKANSE, B. N., TRUNNELL, J. B. and FLUHARTY, R. G.: The effect of total thyroidectomy on functioning of metastatic thyroid cancer. J. Clin. Endocrinol. 8: 826—841, 1948.
34. RAWSON, R. W., SKANSE, B. N., MARINELLI, L. D. and FLUHARTY, R. G.: Radioactive iodine: Its use in studying certain functions of normal and neoplastic tissues. Cancer 2: 279—292, 1949.
35. SCHIFF, L., STEVENS, C. D., MOLLE, W. E., STEINBERG, H., KRUMPE, C. W. and STEVART, P.: Gastric (and salivary) excretion of radio-iodine in man (preliminary report). J. Nat. Cancer Institute. 7: 349—354, 1947.
36. SEIDLIN, S. M., MARINELLI, L. D. and OSHRY, E.: Radioactive iodine therapy. (Effect on functioning metastases of adenocarcinoma of the thyroid.) J. A. M. A., 132: 838, 1946.
37. SEIDLIN, S. M., OSHRY, E. and YALOW, A. A.: Spontaneous and experimentally induced uptake of radio-iodine in metastasis from thyroid carcinoma: a preliminary report. J. Clin. Endocrinol. 8: 423—432, 1948.
38. SEIDLIN, S. M., ROSSMAN, J., OSHRY, E. and SIEGEL, E.: Radio-iodine therapy of metastases from carcinoma of the thyroid: A six year progress report. J. Clin. Endocrinol. 9: 1122—1137, 1949.
39. SOLEY, M. H. and MILLER, E. R.: Treatment of Graves' Disease with radioactive iodine. M. Clin. North Am., 32: 3—17, 1948.
40. SKANSE, B.: Radioactive iodine in the diagnosis of thyroid disease. Suppl. 235. Acta med. Scand., 1949.
41. STRANDQVIST, M.: Studien über die kumulative Wirkung der Röntgenstrahlen bei Fraktionierung. Acta Radiologica, Suppl. 55, 1944.

42. TRUNNELL, J. B., MARINELLI, L. D., DUFFY, B. J., HILL, R., PEACOCK, W. and RAWSON, R. W.: The treatment of metastatic thyroid cancer with radioactive iodine: credits and debits. J. Clin. Endocrinol. 9: 1138—1152, 1949.
43. TRUNNELL, J. B., RAWSON, R. W., MARINELLI, L. D. and HILL, R.: The effect of thyroid stimulating hormone on the function of human normal and malignant thyroid tissue. J. Clin. Endocrinol. 8: 598, 1948.
44. WILLIAMS, R. H.: Antithyroid drugs IV: Comparison of results of newer forms of treatment of thyrotoxicosis. Arch. Int. Med. 80: 11—36, 1947.
45. WILLIAMS, R. H., JAFFE, H., ROGERS, W. F., TOWERY, B. and TAGNON, R.: Reciprocal relationships of radio-iodotherapeusis and thyroid function. (Abstr.) J. Clin. Invest. 24: 562—563, 1948.
46. YAGODA, H.: Radioactive measurements with nuclear emulsions. New York, 1949.

FROM THE ORTHOPEDIC CLINIC OF THE KAROLINE INSTITUTE, STOCKHOLM, SWEDEN
(HEAD: PROFESSOR STEN FRIBERG)

CHANGES IN THE SACRO-ILIAC JOINTS IN MORBUS BECHTEREW AND OSTEITIS CONDENSANS[1]

by

Folke Knutsson

The earliest roentgenological manifestations in morbus Bechterew are changes in the sacro-iliac joints. They appear earlier than arthritides in the intervertrebral joints and earlier than the ligamentous ossifications along the spine. They are, however, preceded by a clinical prodromal stage with diffuse, rheumatic pains in the back and extremities which can continue for years or shorter periods. This clinical prodromal stage is usually so ambiguous that one cannot make a definite diagnosis of Bechterew's disease until the typical changes in the sacro-iliac joints are fully developed.

In order that the roentgenologist may be able to contribute to the making of as early a diagnosis as possible, it is necessary for him to know the character of the initial changes as well as to be certain that similar changes are not due to some other etiology.

In the works dealing with changes in the sacro-iliac joints in Bechterew's disease, the material has consisted of Bechterew patients whose sacro-iliac joints have been subjected to roentgenological observation. I have approached the problem from the opposite direction. I have collected all cases where the roentgenological examination has shown changes in the sacro-iliac joints. The material emanates from the orthopedic clinic belonging to Karolinska Sjukhuset in Stockholm between 1936 and 1949. I have sorted out the cases with tbc, tumours, injuries and septic processes attacking the joint, besides three cases which have had changes in the joint that are not characteristic. The remaining cases are dispersed into two main groups of which the one is composed of destructive arthritis of the kind occurring in morbus Bechterew (147 cases), and the other composed of osteitis condensans (37 cases).

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Morbus Bechterew

It was GILBERT SCOTT, the London roentgenologist, who emphasized the importance of carrying out a routine roentgen examination of the sacro-iliac joints in Bechterew's disease. His first report dates from 1932. He states that typical changes in the sacro-iliac joints are pathognomonic for the disease, that they are present in every case and that they appear earlier than the spinal changes. His published material comprises 500 cases. FORESTIER found that in 153 cases there were only 2 in which changes in the sacro-iliac joints were not discovered. GOLDING found changes in the sacro-iliac joints in every one of his 91 cases.

The importance of roentgenological changes in the sacro-iliac joints is also dealt with in the works of KREBS and WURM, and HERMANN-JOHNSON and LAW. A Swedish work by BRAHME gives a report of 28 cases.

With regard to the arthritic process in the sacro-iliac joints it is possible to discern different roentgenological stages:

1) *The initial stage.* The earliest change is manifested by a certain opacity of the contours of the joint surfaces together with an indication of sclerosis on the iliac side of the joint. The joint space has maintained breadth.

2) *The destructive stage.* The joint space becomes narrow due to cartilaginous destruction. Superficial erosion takes place on the joint surfaces and there is an increase in the juxta-articular sclerosis. Both the appearance of the erosion as well as the more severe sclerosis in this stage mainly embrace the iliac side of the joint.

3) *The ankylosing stage.* The joint space begins to diminsh more and more and ankylosis begins to set in. Finally, ankylosis is fully established. At this stage transformation of the bony structure takes place in the vicinity of the joint, in that the sclerosing disappears and the structure regains a normal character.

With regard to cases where there have been arthritic changes in the sacro-iliac joints, it has been my task to decide whether all the cases could be included in the category morbus Bechterew or whether the arthritis might be due to some other etiology.

1. In 92 cases, of which 7 were women, typical morbus Bechterew changes were found in the spine and the connection is thus clear. Thanks to serial examinations it was possible to study the course of the disease in 15 cases. In these cases an absolutely typical morbus Bechterew has developed by means of which the specific character of the initial changes in the sacro-iliac joint could be verified (Fig. 1, 2).

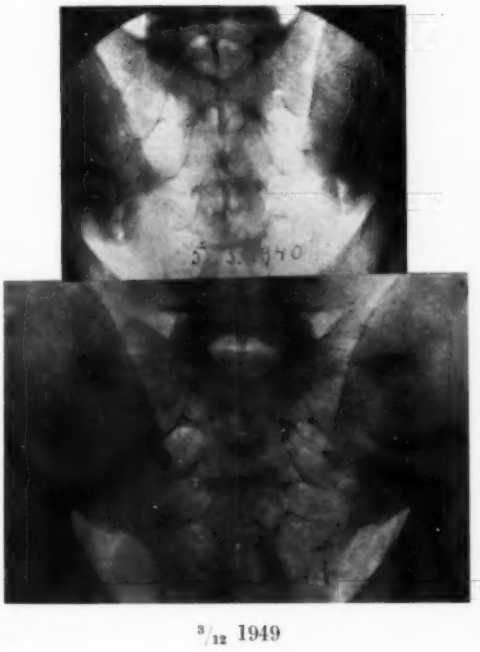


Fig. 1.

Fig. 2.

Fig. 1.

814/40. Man, born 1913. When examined in 1940 a typical arthritis with sclerosis and erosion was found on the iliac side. The patient complained about pain in the back and slight rigidity. E.S.R 22 mm. In 1949 there was ankylosis in both sacro-iliac joints but the sclerosis on the iliac side had disappeared. In the intervertebral joints of the lumbar vertebrae there was ankylosis and in the spine ligamentous ossification.

Fig. 2.

24/505. Man, born 1894. When examined in 1932 there were no changes in the sacro-iliac joints; in 1939 there were marked arthritic changes. One can see on a special picture how the sclerosis and erosion entirely embraces the iliac side. In 1939 partly ligamentous ossification between the vertebral bodies of the lumbar vertebrae and partly arthritis in the intervertebral joints.

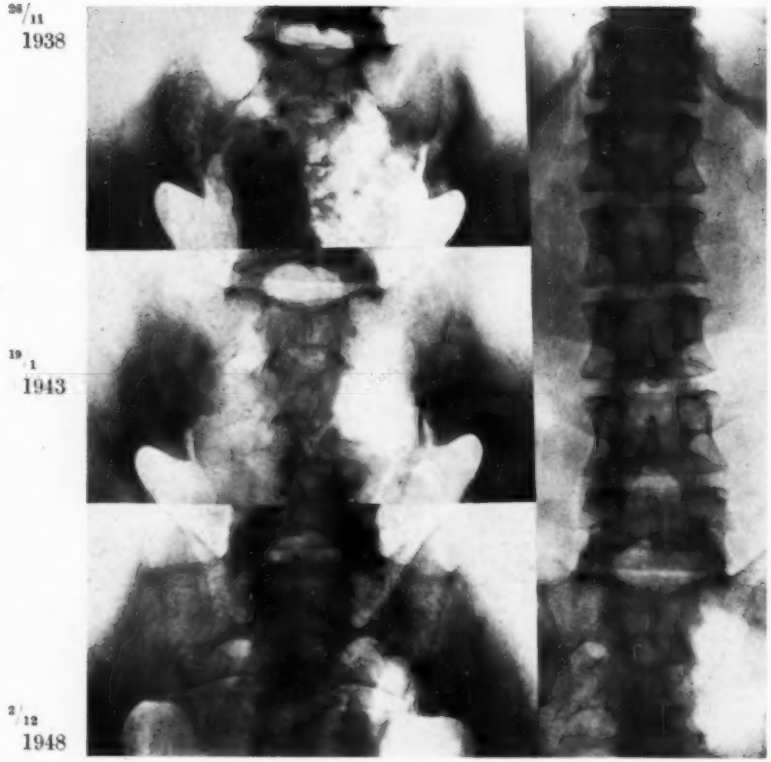
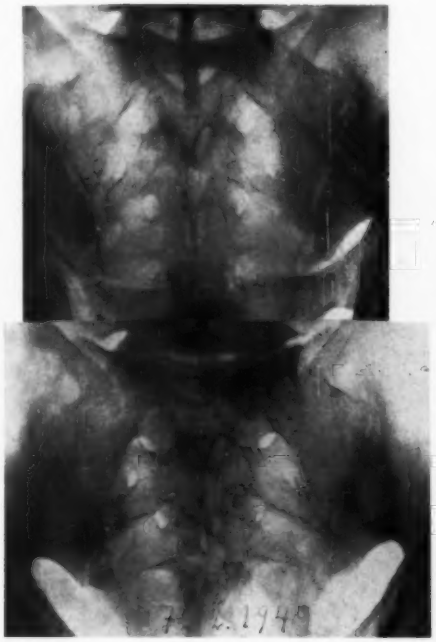


Fig. 3.

1425/38. Man, born 1923. When examined in 1938 no arthritic phenomena were found in the sacro-iliac joints. In 1943 there was a marked arthritis. The patient had good back mobility the whole time. E.S.R. 25 mm in one hour. In 1948 ankylosis was found in the sacro-iliac joints but no roentgenological changes were seen in the lumbar vertebrae. Back mobility somewhat restricted. E.S.R. was 53 mm in one hour. In addition the patient had arthritis in the hip joints. This case can be regarded as being an abortive type. Has not had roentgen treatment or chemotherapy.

2. In 7 cases, all of whom were men (Fig. 3, 4, 5, 6, 7) where roentgenography has shown typical arthritic changes in the sacro-iliac joints, no typical spinal changes were found when they were examined five to eight years later (510/36, 1184/42, 1425/38, 4925/40, 1170/45, 3469/46, 7075/46). The changes in the sacro-iliac joints have gradually progressed and, in three cases, have led to ankylosis. There were no arthritic changes in the intervertebral joints of the spine nor any ligamentous ossification

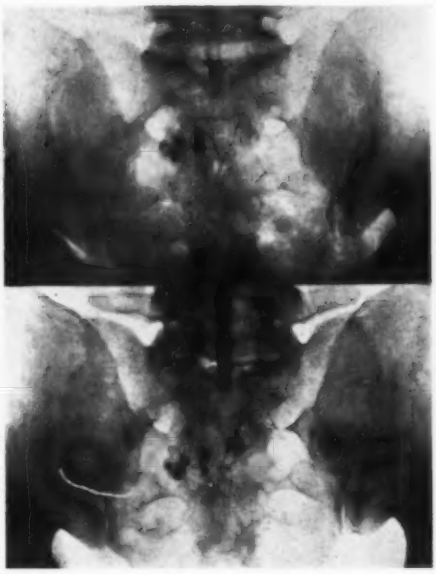
$^{21}/_{11}$ 1940



$^{17}/_{12}$ 1949

Fig. 4.

$^{1}/_{3}$ 1945



$^{17}/_{1}$ 1950

Fig. 5.

Fig. 4.

4925/40. Man, born 1905. When examined in 1940 there was a typical arthritis in the sacro-iliac joints with erosion and sclerosis on the iliac side. The patient complained about low back pains. In 1949 there was still arthritic changes with erosion and cartilaginous destruction. The patient had full mobility in his back and was quite fit for work. There was no ligamentous ossification within the spine nor any signs of arthritis in the intervertebral joints. E.S.R. 28 mm in one hour. Can be regarded as an abortive type. Has not had either consistent roentgen treatment or chemotherapy.

Fig. 5.

1170/45. Man, born 1907. Trouble in his back since 1940 accompanied by diffuse pains. When examined on 1/3/1945 arthritic phenomena were found in both sacro-iliac joints. He then had rigidity and pains in the back and his E.S.R. was 41. When examined on 17/1 1950, the arthritic changes had diminished and the erosion and juxta-articular sclerosis had also diminished. The patient was then totally free from trouble and had normal mobility. Can be regarded as an abortive type. Has not had any consistent roentgen treatment or chemotherapy.

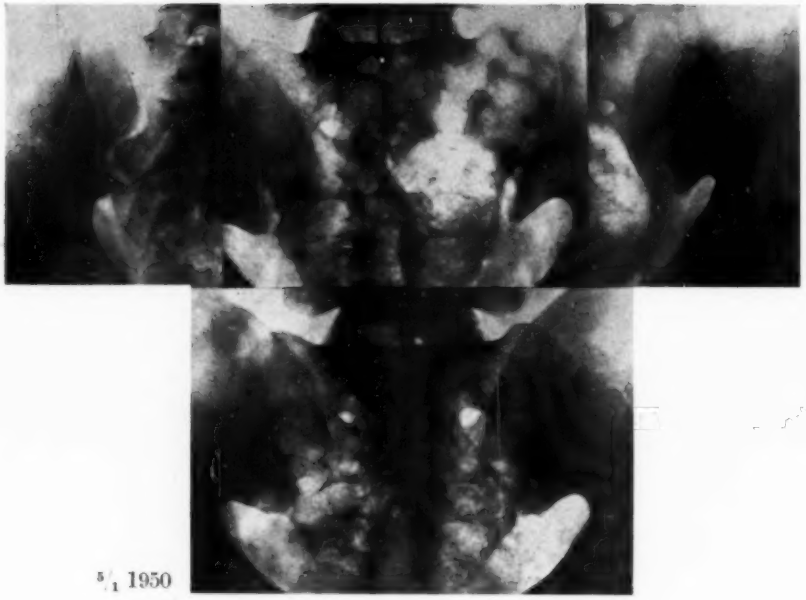


Fig. 6.

1148/42. Man, born 1923. Has had trouble in his back since 1940. E.S.R. has remained between 20 and 30 mm per hour. When examined in 1942 there was a considerable arthritis in the sacro-iliac joints with erosion of the articular surfaces and sclerosis on the iliac side. In 1950 there was a marked cartilaginous destruction and the beginning of ankylosis. The patient had completely normal back mobility. Arthritis in one hip joint. Can be regarded as being an abortive type. Has had neither consistent roentgen treatment nor chemotherapy.

along the spinal column. Spinal mobility has been fully maintained or only slightly minimized. The patients have all been fully capable of doing work but have complained about slight back trouble. E.S.R. has been somewhat raised.

The question is how these arthritic changes should be interpreted in these cases? It is feasible to presume that it could be an *abortive* form of morbus Bechterew. It concerned men who had suffered for a long time from back trouble and whose E.S.R. was raised. The disease has progressed from a prodromal stage and has come to embrace the sacro-iliac joints and then ceased to develop further — there were no changes in the spine. It is conceivable, however, that the disease is not fully cured in this abortive form but that it could continue after further time. These

Fig. 7.

7075/46. Man, born 1926. Ever since 1940 he has had pains in the left leg but no trouble with his back. On several occasions during 1941, his E.S.R. was round about 40 mm. When he was examined on 31/1/1950 his E.S.R. was 5. At that time the patient had no back troubles and his back was normally mobile.

When he was roentgenographed on 23/12/1941, there was arthritis in the left sacro-iliac joint but the right one was normal. On 7/11/1946, there were marked arthritic changes in the right joint with cartilaginous destruction, erosion and juxta-articular sclerosis. At this time the left joint was ankylosed. When examined on 31/1/1950 ankylosis had developed in both sacro-iliac joints.

This case can be regarded as being an abortive type of morbus Bechterew. Has had neighter roentgen treatment nor chemotherapy.

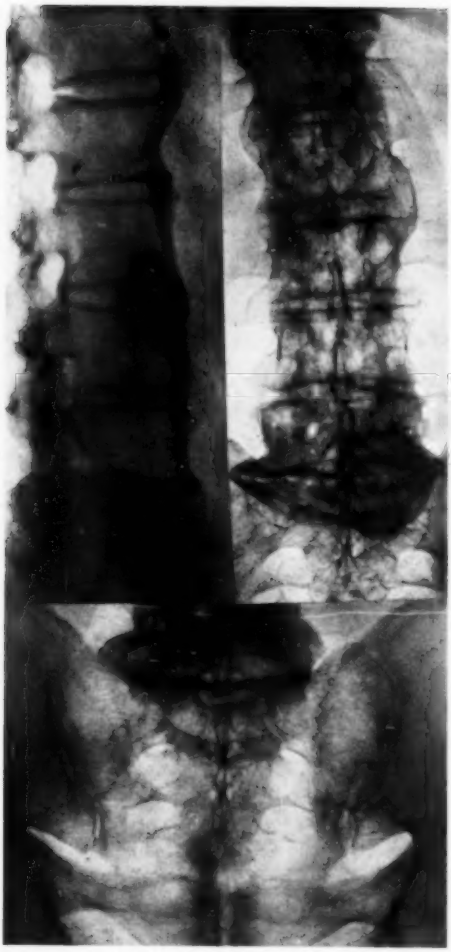


Fig. 8.

20128. Man, born 1880. Has typical morbus Bechterew ligamentous ossification and ankylosis in the intervertebral joints. Both sacro-iliac joints intact.

patients were not given any consistent roentgen treatment nor subjected to any chemotherapy. SCOTT and FORESTIER have pointed out that the development of the disease can come to a standstill during different stages. GOLDING has found: »individuals with pathologic changes in the sacro-iliac joint without spinal changes. They gave a history of the same

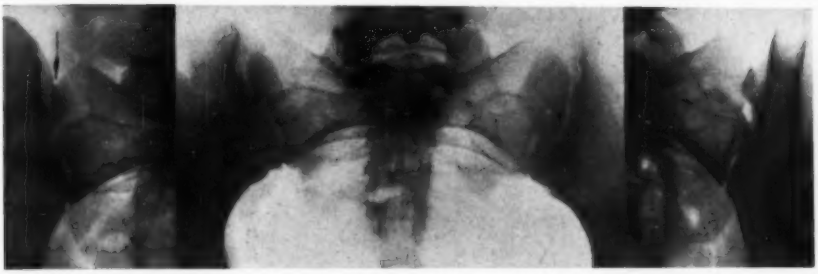


Fig. 9.

2640/38. Woman, born 1908. Complains about pains in the hip regions. An examination shows typical osteitis condensans with sclerosis only on the iliac side of the joint, but with intact joint space.

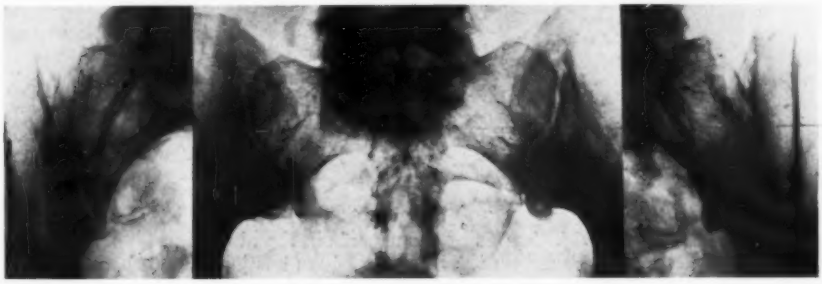
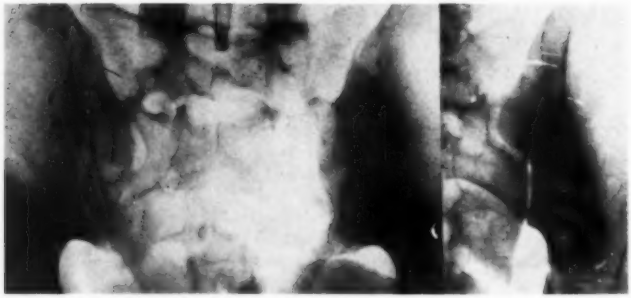


Fig. 10.

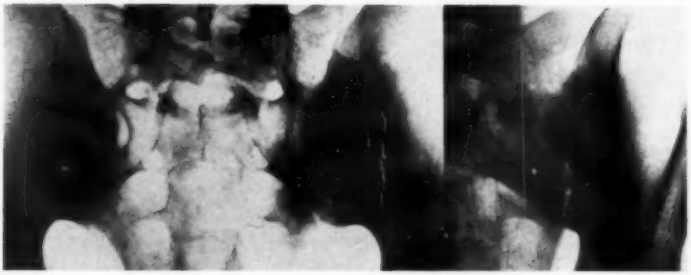
4460/38. Woman, born 1894. Is trouble with pains in the region of the hips. When examined on 20/12/1938 there was arthrosis in both sacro-iliac joints accompanied by juxta-articular sclerosis and lipping of the anterior areas of the edges of the articular surfaces. The joint space is intact. Should be regarded as arthrosis deformans.

type as the 91 patients with spondylitis ankylo-poietica.» It is important to know about cases of this abortive type when it comes to judging the importance of a certain therapeutic measure for preventing further progress of the disease.

3. In 48 cases, of which 13 were women, there were no spinal changes. Here one has been able to consider the disease as being in an early stage with localization in the sacro-iliac joint only. The clinical data gives support to a supposition of this nature. Thus the clinical picture having widespread rheumatic, not characteristic, pains, as well as a rise in the E.S.R. has been found. As we have no knowledge about the further



11/3 1944 Fig. 11 a.



2/12 1947 Fig. 11 b.

Fig. 11 a and b.

1286/44. Man, born 1917. Complains about pains in the hip regions. When examined on 11/3/1944 sclerosis was found on the iliac side of the left joint. Joint space is intact. When examined on 2/12/1947 the joint space was still intact and sclerosis had increased and embraces both the iliac as well as the sacral side. Similar changes have also appeared in the right joint.

development of the disease, it is not possible to say whether the primary diagnosis was justified.

Amongst all the cases of morbus Bechterew there was only one individual case where changes in the sacro-iliac joint has been lacking. This was the case of a man of 66 years of age (20128) who had a long-standing back trouble accompanied by a total rigidity of the back. Roentgenography revealed widespread ligamentous ossification between the vertebrae together with ankylosis in the small joints in a manner so typical of morbus Bechterew (Fig. 8).

Osteitis Condensans Ilii

This disease has got its roentgenological definition from the works of Barsony and Polgár, Berent, Rendich and Schapiro, Schafar,

HARE and HAGGART. The disease is characterized by a more or less widespread and intensive sclerosis within the ilium in the vicinity of the sacro-iliac joint. The joint space is intact. BARSONY and POLGÁR, and RENDICH and SCHAPIRO mention one case where sclerosis was also found within the juxta-articular part of the sacrum. All the authors have found that the disease occurs predominantly in women and only occasionally in men. The etiology is unknown. BERENT is of the opinion that injury to the joint during pregnancy and parturition are significant whilst RENDICH and SCHAPIRO think that the cause lies in mild inflammation. It is thought that the disease might cause pains in the back and hips. Knowledge about the development of the disease on the basis of serial examinations is lacking.

There are 37 cases of osteitis condensans in my material of which 35 are women and 2 are men. It is bilateral in 32 cases and unilateral in 5.

In 32 cases the sclerosis is restricted entirely to the iliac side and the roentgen picture gives full support to the report given by the previous authors. In these cases the joint space is intact and the articular surfaces are without changes (Fig. 9).

In 5 cases, however, there is also sclerosis on the sacral side and in these cases it is sometimes possible to find that the edges of the articular surfaces have lip-shaped projections and that the joint space is somewhat narrower than normal. These roentgenological changes justify one in classifying the disease as arthrosis deformans (Fig. 10).

As a rule it is necessary to take oblique pictures of the sacro-iliac joints so as to be able to localize the sclerosis in relation to the joint space. If, on such oblique pictures, the projection is directed obliquely caudal instead of directly vertical, the anterior part of the joint will be represented tangentially. It is in such projections that the lip-shaped edges of the articular surfaces are most clearly noticed.

In other cases, one finds marked sclerosis on both the iliac and the sacral side of the joint; the joint space is somewhat narrow but there are no lip-shaped protrusions on the edges of the articular surfaces (Fig. 11).

It is not possible to determine whether these three types of changes are fundamentally different kinds or whether it is merely a matter of a variation in degree.

The material does not contribute to the knowledge we have about the progress, etiology or clinical significance of the disease as a cause of subjective troubles.

Differential Diagnosis

As a rule it is easy to differentiate between the changes in the sacro-iliac joints that occur in morbus Bechterew and osteitis condensans. There are, however, border cases with insignificantly developed sclerosis

on the iliac side and with seemingly intact joint spaces in which, in the early stages, it can be impossible to make a differential diagnosis. First after a lapse of time, when the changes have become more established, it is possible to make a definite diagnosis.

SUMMARY

The author's material comprises cases having roentgenological changes in the sacro-iliac joints during the period 1936—1949 (Orthopedic Clinic, Stockholm). Changes due to tbc, injuries, septic processes and tumours have been eliminated. In addition to this, three cases having changes which are not characteristic have been removed and not brought into the discussion. The remaining cases are dispersed into two main groups *i. e.* morbus Bechterew (147 cases), and osteitis condensans ilii (37 cases).

Morbus Bechterew. The material comprises 92 verified cases of which 85 are men and 7 are women. The changes in the sacro-iliac joints described are specific for the disease. In no case has such arthritis been found where there has been reason to suppose any other etiology. In one case, only one of the sacro-iliac joints was affected whilst in the remaining cases both joints were affected. The author has pointed out the occurrence of abortive cases where only the sacro-iliac joints were attacked and where the spine was not affected, 7 cases. (In the material for morbus Bechterew, only one case having the sacro-iliac joints free from changes is included.)

Osteitis Condensans. This has occurred in 35 women and 2 men. In 32 cases the typical sclerosis has embraced the iliac side of the joint. In 5 cases sclerosis was also found on the sacral side and, in certain cases, there were lip-shaped protrusions on the edge of the articular surface for which reason the changes could be classified as arthrosis. The material does not justify any conclusions being arrived at in regard to the etiology or clinical significance.

ZUSAMMENFASSUNG

Verf.s Material besteht aus sämtlichen Fällen mit röntgenologischen Veränderungen der Sacroiliacagelenke aus der Orthopädischen Klinik zu Stockholm in den Jahren 1936—1949. Durch Tuberkulose, Verletzungen, septische Prozesse oder Tumoren bedingte Veränderungen schieden aus. Ausserdem sind 3 Fälle mit uncharakteristischen Veränderungen aussortiert und nicht mit erörtert worden. Die übrigen Fälle verteilen sich auf zwei grosse Hauptgruppen, nämlich Morbus Bechterew (147 Fälle) und Osteitis condensans ilii (37 Fälle).

Morbus Bechterew: Das Material umfasst 92 bestätigte Fälle, 85 Männer und 7 Frauen. Die beschriebenen Veränderungen in den Sacroiliacagelenken sind für dieses Leiden spezifisch. In keinem Falle hat eine Arthritis dieser Art vorgelegen, wenn man Grund hatte, eine andere Ätiologie anzunehmen. Bei einem Falle war nur das eine Sacroiliacagelenk verändert, bei allen übrigen beide. Verf. hat auf das Vorkommen von Abortivfällen aufmerksam gemacht, bei denen nur die Sacroiliacagelenke angegriffen sind, während die spinale Beteiligung fehlt, 7 Fälle. (Im Material an Morbus Bechterew ist nur ein einziger Fall vorhanden, bei dem die Sacroiliacagelenke von Veränderungen frei sind.)

Osteitis condensans kam bei 35 Frauen und 2 Männern vor. In 32 Fällen betraf die typische Sklerose die iliakale Seite des Gelenks. In 5 Fällen lag auch an der sakralen Seite eine Sklerose vor, und die Ränder der Gelenkflächen zeigten in gewissen Fällen Lippenbildungen, so dass die Veränderung als Arthrose zu bezeichnen war. Das Material ermöglicht keine Schlussfolgerungen inbezug auf Ätiologie oder klinische Bedeutung.

RÉSUMÉ

Le matériel de l'auteur est formé de l'ensemble des cas présentant des lésions radiologiques des articulations sacro-iliaques qui furent observés pendant la période de 1936 à 1949 (Clinique Orthopédique de Stockholm). Il en a élimine les lésions par tbc., accidents, processus septiques et tumeurs. De plus, il a exclu de la discussion trois cas avec des altérations non caractéristiques. Les observations restantes se répartissent en deux grands groupes principaux, à savoir la maladie de Bechterew (147 cas) et l'ostéite condensante de l'os iliaque (37 cas).

Maladie de Bechterew. Le matériel comprend 92 cas vérifiés, soit 85 hommes et 7 femmes. Les altérations décrites des articulations sacro-iliaques sont spécifiques pour l'affection. Dans aucun cas on n'a rencontré d'arthrite où il y ait eu lieu d'admettre une autre étiologie. Dans un cas l'une seulement des articulations sacroiliaques était touchée, dans tous les autres le mal était bilatéral. L'auteur a attiré l'attention sur l'existence de formes abortives où seules les sacro-iliaques sont attaquées, sans participation du rachis, ce qu'il a vu 7 fois. (Dans le groupe du Bechterew il n'y a qu'un seul cas isolé, où les sacro-iliaques soient indemnes de modifications.)

L'ostéite condensante a été observée chez 35 femmes et deux hommes. Dans 32 cas la sclérose typique atteignait le côté iliaque de l'articulation. Dans 5 elle existait aussi du côté sacré, et certaines fois les bords des surfaces articulaires étaient garnis de formations labiées, de sorte qu'il fallait parler d'arthrose. On n'est pas justifié à tirer de ce matériel des conclusions touchant l'étiologie ni la signification clinique.

LITERATURE

Barsony and Polgár: Osteitis condensans ilii. Fortschr. a. d. Geb. Röntgenstr. 37, 1928.

Berent: Beiträge zur Pathologie der Kreuzdarmbeinfugen. Arch. f. Orthop. u. Unfall-Chir. 32, 1933.

Brahme: Nordisk Medicin, Stockholm 1948.

Forestier: The Importance of Sacro-Iliac Changes in the Early Diagnosis of Ankylosing Spondylarthritis. Radiology 33, 1939.

Golding: Spondylitis Ankylo-poietica. Brit. J. Surg. 23, 1935—36.

Hare and Haggart: Osteitis condensans ilii. J. A. M. A. 128, 1945.

Hermann-Johnson: Ankylosing Spondylitis, London 1949.

Krebs: Das Röntgenbild des Beckens bei der Bechterewschen Krankheit. Fortschr. a. d. Geb. Röntgenstr. 1934.

— Die Bechterewsche Krankheit, Dresden 1938.

Rendich and Schapiro: Osteitis condensans ilii. J. Bone and Joint Surg. 18, 1936.

Schafar: Osteitis condensans ilii. The Lancet 235, 1938.

Scott: Adolescent Spondylitis, London 1942.

NEWS ON THE BOOKSHELF

Malignant Disease and Its Treatment by Radium, Volumes II & III, by *Sir Stanford Cade*. Second Edition. John Wright & Sons Ltd., Bristol. Price: 52/6 per volume.

Morgagni's Syndrome — Hyperostosis Frontalis Interna, Virilismus, Obesitas — by *Folke Henschen*. Oliver & Boyd Ltd., Edinburgh 1949. Price 30/—.

Carcinoma of the Larynx by *F. Baclesse*, British Journal of Radiology, Supplement No. 3. London 1949. Price 25/—.

Précis de Technique Radiologique par *A. Nègre & F. Rouquet*. G. Doin & Cie, Paris 1949.

Aperçus Roentgenthéraphiques relatifs à Divers Modes d'Involution Cancéreuse et Méthodes de Protection par *Henri Coutard*. G. Doin & Cie, Paris 1949.

Neuroradiology by *Alexander Orley*. Charles C. Thomas, Publishers, Springfield, Ill., U. S. A., 1949. Price: $ 11.50.

The 1949 Year Book of Radiology. The Year Book Publishers, Inc., Chicago. Price: $ 6: 50.

Bronchography by *Eelco Huizinga & G. J. Smelt*. Van Gorcum & Comp., Assen, Netherlands, 1950. Price: Hfl. 39: —.

Confrontations Radio-Anatomo-Cliniques. Fascicule III. Publiées sous la direction de *M. Chiray, R. A. Gutmann & J. Sénèque*. Masson & Cie, Paris.

Coxitis tuberkulosa. Ein Beitrag zur röntgenologischen Pathologie der Skelettuberkulose von *Herbert Gardemin*. Sonderband 26 zur Strahlentherapie. Urban & Schwarzenberg, Berlin & München 1950. Preis: DM 15:—, geb. DM 18:—.

A Text-Book of X-Ray Diagnosis by *British authors*. Edited by *S. Cochrane Shanks & Peter Kerley*. In 4 volumes. Second Edition. H. K. Lewis & Co., Ltd , London. Price 60/—.

Der Ultraschall in der Medizin. Kongressbericht der Erlanger Ultraschall-Tagung 1949. S. Hirzel Verlag, Zürich 1949.

Lehrbuch der Röntgendiagnostik von *H. R. Schinz, W. E. Baensch, E. Friedl & E. Uhlinger*. Bd I: Skelett. 5. neu bearb. Aufl. Georg Thieme Verlag, Stuttgart 1950. Preis: DM 66: —.

Die klinische Röntgendiagnostik der inneren Erkrankungen von *Prof. Dr. Herbert Assmann*. Sechste Auflage. Erster und zweiter Teil. Springer Verlag, Berlin-Göttingen-Heidelberg 1950. Preis: Erster Teil DM 56: —, geb. DM 59: 60; Zweiter Teil DM 72: —, geb. DM 75: 60.

Lehrbuch der röntgenologishen Differentialdiagnostik von *W. Teschendorf*. 2. verm. u. verb. Aufl. Bd I: Erkrankungen der Brustorgane. Preis: Ganzleinen DM 84: —. Bd II: Erkrankungen der Bauchorgane. Preis: Ganzleinen DM 72:—.

Tabellen zur Dosierung der Röntgenstrahlen von *Leonard Grebe & Werner Wiebe*. Sonderband 25 zur Strahlentherapie. Urban & Schwarzenberg, Berlin & München 1950. Preis: DM 15: —, geb. DM 18: —.

PRESENTATION OF RESULTS OF TREATMENT OF CANCER[1]

by

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The main object in presenting results of treatment of cancer is to submit to Public Health authorities and to the medical profession reliable information as to what can be achieved in the fight against cancer.

Public Health agencies are chiefly interested in the gross result of treatment of cancer as a whole and also of its individual types; reliable information is obtained from large series of uniformly registered cases of cancer representing a total population of a country or province; actuarial methods are used to eliminate sources of error. For the time being a statistical investigation of the mentioned type constitutes a problem of national character since in many countries the reporting on cancer material is not yet organized.

The medical profession is chiefly interested in comparing and evaluating the results obtained by different methods of treatment since a precise knowledge of results is essential to the development of any form of therapy. Comparison of results to be of value requires not only a reliable and uniform registration of the cases but, in addition, that the series to be compared are, in fact, comparable. This is the more important since, as a rule, small series of cases only are available and since errors due to differences in the clinical quality of the material must be eliminated before applying statistical research methods.

Securing of comparability is a problem of international character, complicated by all the difficulties inherent in any form of international cooperation.

In the following I shall deal mainly with problems relating to comparability. Illustrative reference will be freely made to the »Annual Reports on the Results of Radiotherapy in Cancer of the Uterine Cervix» as an international attempt at uniformity in this particular field.

Comparability requires:

(A) that the type of cancer is strictly defined;

(B) that the figures to be compared refer to material of equal clinical quality in respect to curability;

(C) that — where unselected material is not available — the differences caused by selection should be eliminated to the greatest possible extent;

(D) that all data concerning clinical material are recorded in an identical manner;

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(E) that the different categories of end results in which treated patients should be placed are satisfactorily defined; and

(F) that in calculating the results of treatment suitable and identical methods of evaluation are used.

A. Definition of the type of cancer to be reported on

Precise definitions are fundamental to both reliability and comparability.

Experience has shown that a correct classification of all cases of cancer of the uterus necessitates a system of detailed character. In primary cancer of the uterus two different types are generally recognized: Cancer of the corpus and Cancer of the cervix. The collaborators in the Annual Reports are requested to differentiate between the following types.

(1) Cancer of the corpus;
(2) Cancer of the cervix;
(3) Cancer of the corpus and endocervix;
(4) Cancer of the uterus and ovary;
(5) Cancer pelvis.

} primary site of origin unknown.

It would vitiate comparability if at one clinic the cases of type (3), (4) and (5) were registered as corpus cancer whereas at another clinic they were registered as cancer of the cervix.

Similar problems, perhaps even more difficult to solve are frequently encountered in differentiating anatomically between various neoplasms of adjoining regions for instance in cancer of the oral cavity, cancer of the pharynx and the larynx whereas it may be easier to define anatomically what should be understood by cancer of the breast, cancer of the penis, cancer of the lip and others.

In many types of cancer the important work on uniform definitions has not even begun.

B. Differences in the clinical quality of the material

The greatest difficulty in securing comparability is due to the fact that the samples of patients suffering from cancer and treated at different centres are not of equal clinical quality.

Table 1 demonstrates the proportion of cases of cervical cancer allotted to the different stages of disease at 22 centres in 8 different countries.

It may be noted that the percentage of Stage I cases varies from 2.9 to 29 per cent. Similarly, Stage III shows a variation from 69.6 to 11.8 per cent.

There are numerous reasons for these marked differences. Broadly speaking, the main cause of the differences lies in the fact that for some clinics the material is not selected, for others there is a varying degree of selection.

Over-all rates calculated on selected material will not provide reliable information as to what can be achieved by treatment, nor is it possible to draw reliable conclusions as to the value of the different methods of treatment by comparing selected and unselected material.

Available material shows that selection is less pronounced at centres responsible for the accomodation and treatment of all patients within a geographically defined area. The sample of patients at such a centre may be considered as random and unselected provided all cases of the disease in question occurring within the area are included. Over-

Table 1

Proportion of early and advanced cases of cancer of the cervix uteri treated at 22 radiotherapeutic centres in 8 different countries in 1936 to 1941 inclusive.

	Number of patients treated	St. I %	St. II %	St. III %	St. IV %
1	648	2.9	14.0	69.6	13.4
2	1 279	4.6	43.5	28.3	23.6
3	370	5.9	27.3	55.7	11.1
4	437	6.6	35.9	41.2	16.2
5	1 579	9.5	51.2	29.9	9.4
6	491	11.2	38.3	36.9	13.6
7	298	11.4	26.2	36.6	25.8
8	1 338	12.1	36.8	36.1	19.4
9	275	12.7	42.9	33.5	10.9
10	496	12.9	37.9	40.1	9.1
11	112	13.4	31.3	42.0	13.4
12	247	13.4	35.6	36.0	15.0
13	1 513	16.1	42.0	31.9	10.0
14	674	17.8	53.4	20.6	8.2
15	457	18.6	42.7	34.1	4.6
16	360	21.4	43.6	30.0	5.0
17	164	24.1	40.8	22.8	12.0
18	161	22.4	62.7	11.8	3.1
19	753	22.6	35.3	37.1	5.0
20	643	23.3	28.3	33.0	15.4
21	209	27.8	26.8	26.8	18.7
22	205	29.0	30.0	34.2	6.8

all rates calculated on series of this character may provide reliable information as to the value of treatment and may be compared with similar rates at similarly organized centres.

Centres of this character — other centres but exceptionally — should be justified in stating what is called an absolute cure rate. Of 24 collaborators in Volume 5 of the Annual Reports only 10 fall into this category.

There is every reason to believe that conditions are similar in other types of cancer and that consequently the great majority of presented over-all rates are not comparable.

C. Elimination of differences caused by selection

In the absence of comparable over-all rates it becomes necessary to resort to other methods such as the stage rate. In the instance of cervical cancer stage-grouping helps to obtain comparable material for a statistical evaluation of the results of treatment

Stage-grouping to be of value requires

— that the definitions of the different stage-groups should be as simple and precise as possible;

— that the rules for allocating cases to their appropriate stages should be easily interpreted and should offer ample opportunity for being applied in a uniform way by the examining clinicians;

— that one stage should be differentiated from the other by characteristics easily recognized on clinical examination even by a less experienced examiner;

— that the system of grouping should be sufficiently complete to include every possible type of case;

— that each stage-group should contain a number of cases sufficient for a statistical evaluation of the result within that particular group.

In spite of considerable efforts universal agreement on stage-grouping in cancer of the cervix has not yet been reached. Most of the leading radiotherapeutic centres in Europe have adopted the so called League of Nations classification by which the cases are divided in four stage-groups, according to the anatomical extent of the growth. The system has often been criticized. However, so far no other classification has been suggested that would seem to fulfill the above requirements.

In stage-grouping of cancer of the cervix the anatomical extent of the growth was chosen as the decisive factor. Other factors which are of importance in respect to curability may have to form the basis for grouping in other types of cancer, *e. g.*

(1) the site of the growth within the organ involved for example anterior two thirds compared to posterior one third of the tongue;
(2) the presence or absence of lymph-node metastases;
(3) the microscopic appearance; the difference in the prognosis in various histological types of cancer of the ovary may serve as an example.

This brief review indicates that, to fulfill the requirements mentioned above, a classification system for different types of cancer needs separate consideration for each type, expert knowledge and intimate collaboration between the clinician, the pathologist and the anatomist. In some types of cancer even the experts may find it difficult to deal with this problem, the solution of which is essential as far as reliability and comparability of statistics is concerned.

Stage-grouping has numerous inherent defects, and complete uniformity in stage-grouping is probably unattainable. However, it provides the only means available at present for obtaining comparable material. Unfortunately time does not permit further discussion.

D. Recording of data in an identical manner

In suggesting rules and regulations for the recording of data a number of factors should be considered.

(1) *Microscopic diagnosis.*

Collaborators in the Annual Reports are requested to exclude the following types of case

a) precancerous conditions, non invasive carcinoma and similar conditions;
b) chorioepithelioma, sarcoma, malignant mixed tumours;
c) cases without microscopic verification alive without evidence of the disease at the end of the 5-year period;

The necessity of microscopic verification has gradually become more completely accepted. Specific rules are required in special instances as:

(i) when, as often happens, a piece of tissue is removed from the periphery of the growth where there are no definite microscopic signs of cancer and yet the malignant character seems evident; cancer of the lip and papillomatous tumours of the oral cavity may serve as typical examples;
(ii) in cases in which it may be difficult to perform a biopsy as, for instance, in cancer of the larynx, the oesophagus, the rectum and the urinary bladder;
(iii) in cases difficult to classify because of differences of opinion among pathologists as to how to differentiate between definitely malignant and potentially malignant neoplasm; there are numerous cases of this type in cancer of the breast, the salivary glands and the ovary.

The present lack of agreed rules for histological classification prevents the presentation of comparable statements in many types of cancer.

(2) *Stage-grouping.*

In addition to what is mentioned above it should be stipulated that stage-grouping should be based on clinical examination prior to treatment, and should not be altered because of later observations made at operation or autopsy.

Different rules are required for tumours which are treated by preoperative irradiation plus surgery.

(3) *Untreated patients.*

Collaborators in the Annual Reports are requested to report on all cases examined at the clinic with a view to treatment whether treated or not. When reporting on the achievement of treatment in any type of cancer this should be made a general rule.

E. Defining of categories in which treated patients are placed

In the Annual Reports it is stipulated

(1) that the annual statement should relate to the total number of patients whose treatment was begun during the year to which the statement relates;
(2) that the result of treatment should relate to the patient's condition after the expiring of a period of observation of at least five years from the beginning of the treatment;
(3) that treated patients at the end of the five year period should be referred to either of the following four groups, namely
   (a) alive without evidence of the disease, including patients successfully treated for recurrence during the period;
   (b) alive with cancer present;
   (c) died from cancer, *i. e.* the cancer for which treatment was given;
   (d) lost sight of;
   (e) died of intercurrent disease;
(4) that freedom from evidence of disease at the end of the 5-year period should be ascertained to the greatest possible extent by examination of the patient at the reporting clinic.

The following items are of special importance.

(1) A 5-year period of observation is considered particularly suitable in cancer of the cervix because by that time the condition has become relatively static.

For each individual type of cancer the most suitable observation period should be determined. In some types it may be preferable to choose a shorter period, in others a longer one. The longer the period the more definite is the result. It should, however, be noticed that the number of patients dying from intercurrent disease and those lost sight of will increase with the length of the period, and that this may reduce comparability. However, this source of error is likely to be eliminated by applying statistical research methods.

(2) The result of treatment may be stated as either a cure rate or a survival rate.

The cure rate is calculated on the number of patients alive without evidence of the disease, the survival rate on the patients alive. Both rates have their advantages and disadvantages. It is less complicated to state correctly the survival rate than the cure rate

since the latter requires careful follow-up, frequently by a specialist. In spite of these disadvantages the collaborators in the Annual Reports are requested to state the cure rate for the following reasons. Most patients suffering from cancer of the cervix are treated by irradiation; the difference between survival and cure rate amounts to about 5 per cent. Consequently, the cure rate offers a more precise information as to what really has been achieved.

In addition, a constant and close control is not only important to the development of therapy but also of benefit to the individual patient and should therefore be encouraged.

Conditions may vary considerably in different types of cancer and in different countries. The choice between survival and cure-rate is a delicate problem.

F. Calculation of results of treatment

In the Annual Reports three different cure rates are presented: (1) the absolute cure rate which is the proportion of cured patients expressed as a percentage of the total number examined; (2) the over-all relative cure rate which is the proportion of cured patients expressed as a percentage of the total number treated; and (3) the stage rates. The absolute rate and the stage rates are discussed above. The over-all relative rate is of value to the individual centre for comparing the results obtained at different periods or by different methods of treatment employed at the centre. A comparison of over-all relative rates presented by different centres is not justifiable unless it is ascertained by a detailed examination that the material to be compared is of equal clinical quality. This will probably occur only very exceptionally.

In future Reports the term cure rate will be exchanged for apparent recovery rate as recommended by the Sub-committee on the Registration of Cases of Cancer of the Expert Committee on Health Statistic of the WHO.

In the Annual Reports it is stipulated that only samples containing at least 100 cases should be accepted for publication the reason being that in samples containing less than 100 cases chance variations are so great that statistically significant differences occur only exceptionally.

As a matter of fact even in samples of 100 cases great care should be observed in drawing conclusions.

Table 2

Probability of difference in cure rates due to random fluctuations only. (The figures shown are for two hypothetical series each of about 100 cases of identical clinical quality. a different method of treatment having been used in each series with a cure rate between 40 and 60 %.)

Observed difference in cure rate Per cent	Probability of a random difference equal to or larger than the one observed Per cent
12.0	10
9.2	20
7.5	30
6.0	40
4.9	50
3.8	60
2.8	70
1.8	80
0.9	90

In Table 2 placed at my disposal by the Swedish statistician Dr. C. O. SEGERDAHL, modern statistical methods are applied. The table is based on the following conditions: Two hypothetical series each of about 100 cases, identical clinical quality; a different method of treatment having been used in each series with a cure rate between 40 and 60 %. It is obvious that unless the difference in the observed rates amounts to at least 6 % no definite conclusions can be drawn as to the comparative value of the two methods. Even at a difference of 6 % there is still a chance of 40 % that the difference is random and not due to the superiority of one method to the other.

It is a constant phenomenon that far reaching conclusions are drawn from insignificant figures when comparing results of treatment of cancer. Such unjustifiable conclusions only bring discredit upon the good name of clinical cancer research and should be avoided. International co-operation of the type of the Annual Reports constitutes a practicable way for the purpose.

SUMMARY

Reliable information concerning the results of treatment of cancer is essential to the development of therapy. Only by comparing results is it possible to estimate the relative value of different methods of treatment.

Comparability requires uniformity in recording of all necessary data, uniformity of stage-grouping in order to provide primary material of equal clinical quality, and uniform rules for calculating the results. Securing of comparability involves numerous problems of different character. They vary with the different types of cancer and should be settled separately for each individual type.

There is, for the time being, a noticeable lack of comparability between the results presented from different clinics. Lack of comparability must be reduced to a minimum before it can be asserted that differences between stated results are due to differences in the methods employed. There is also a lack of critical care in evaluating different methods of treatment by drawing conclusions from insufficient material and insignificant differences.

Minor efforts only have been made to secure comparability. In many types of cancer the work has not even begun. The problems involved are numerous and many of them are difficult to solve. Such facts should not deter us from trying to substitute sound bookkeeping for the present unsatisfactory situation. It is an unfortunate weakness in clinical medicine that statistical research in the results of treatment has been left behind.

ZUSAMMENFASSUNG

Zuverlässige Auskünfte über die Ergebnisse der Krebsbehandlung sind für die Entwicklung der Therapie überaus wichtig. Nur durch Vergleich der Ergebnisse lässt sich der relative Wert der verschiedenen verwendeten Behandlungsmethoden schätzen.

Vergleichbarkeit erfordert Gleichförmigkeit in der Wiedergabe aller erforderlichen Daten, Gleichförmigkeit der Gruppierung in Stadien, um ein Ausgangsmaterial von gleicher klinischer Qualität zu erhalten, sowie gleichförmige Prinzipien für die Berechnung der Ergebnisse. Die Sicherung der Vergleichbarkeit umfasst zahlreiche Probleme verschiedener Art. Diese wechseln mit den verschiedenen Krebstypen und müssen für jeden Typus gesondert festgestellt werden.

Zur Zeit sind die von verschiedenen Seiten gemeldeten Ergebnisse deutlich unvergleichbar. Diese Fehlerquelle muss auf ein Minimum herabgedrückt werden, ehe als festgestellt gelten kann, dass Unterschiede der gemeldeten Erfolge durch Unterschiede der

verwendeten Methoden bedingt sind. Es herrscht auch eine merkbare Nachlässigkeit bei der Bewertung verschiedener Behandlungsmethoden, indem aus insignifikanten Zahlen Schlussfolgerungen gezogen werden.

Es sind nur geringe Anstrengungen gemacht worden, Vergleichbarkeit zu erzielen, und bei vielen Krebstypen hat die Arbeit nicht einmal begonnen, denn es ist eine unglückselige Schwäche der klinischen Medizin, dass statistische Erforschung der Behandlungsergebnisse hintangesetzt worden ist. Die damit verbundenen Probleme sind zahlreich, und viele derselben sind schwer zu lösen, aber solche Umstände dürfen uns nicht davon abhalten zu versuchen, die heutige unbefriedigende Lage mit stichhaltiger Buchführung zu ersetzen.

RÉSUMÉ

Il est essentiel de connaître de façon sûre les résultats du traitement du cancer si l'on veut voir se développer la thérapeutique de ce mal. C'est seulement en confrontant des résultats obtenus qu'on peut établir la valeur comparative des diverses méthodes de traitement mises en œuvre.

Pour pouvoir faire des comparaisons il faut de l'uniformité dans l'enregistrement de toutes les données nécessaires, de l'uniformité dans le groupement par stades afin de fournir un matériel de base qui ait partout la même valeur clinique, enfin de l'uniformité dans les règles à suivre pour le calcul des résultats. Rendre possibles les comparaisons, celà pose de nombreux problèmes, de diverse nature. Ils varient avec les différents types de cancer, et chacun d'eux réclame une solution particulière.

A l'heure actuelle il existe un manque de comparabilité prononcé entre les résultats provenant de différentes cliniques. Cette cause d'erreur doit être réduite à un minimum avant de pouvoir affirmer que les différences dans les résultats soient dues aux différences dans les méthodes employées. C'est aussi avec une insouciance notable qu'on juge de la valeur des diverses méthodes de traitement en tirant des conclusions de chiffres sans signification.

On n'a fait que de faibles efforts pour assurer une comparabilité, et en ce qui concerne beaucoup de types de cancer ce travail n'a même pas été commencé, car une infirmité malheureuse de la médecine clinique consiste à avoir laissé à l'arrière-plan les recherches statistiques sur les résultats thérapeutiques. Les problèmes posés sont nombreux, et beaucoup d'entre eux sont difficiles à résoudre, mais cela ne devrait pas nous empêcher de chercher à substituer une «comptabilité» solide à la pratique peu satisfaisante de la situation actuelle.

Index to Volume XXXIII

Roentgen Diagnostics

Nervous System

Pag.

Angiography of vertebral artery 389

Digestive Tract

Gastric examination by fluorographic methods 49
Prolapse of gastric mucosa into duodenum 69
Acute abdominal distension 104
Die nichtgefüllte Gallenblase 115
Small-cystic diverticulosis of gallbladder 147
Atresia of esophagus 529
Rod-shaped gall stone 535

Heart and Vessels

Developmental anatomy of heart 131
Angiography of vertebral artery 389
Patent ductus arteriosus 405
Experimental embolism 507

Lungs, Pleura and Mediastinum

Bronchusadenom 187
Experimental pulmonary embolism 507

Diseases and Fractures of Bones and Joints

Metopic suture 1
Hereditary congenital abnormalities 41
Multiple myeloma 515
Sacro-iliac joints 557

Radiotherapy

Remissions in Hodgkin's disease 31
Use of radioactive substances in Sweden .. 281
Kollumkarzinom 412
Hodgkin's disease and pregnancy 427
Multiple myeloma 515
Radioactive iodine in thyroid carcinoma .. 539
Presentation of results of treatment of cancer 571

Technique

Roentgen Examination

Printing of negatives on paper 83
Bronchography 421

Radiotherapy

Dose calculator for radioactive sources .. 17
Radon purification 311
Pag.
Intense roentgen radiation of short duration 328
Beryllium window tube 435

Protection and Injuries

Periodical inspection of therapy installations 253
Protection of living organism against roentgen rays 296
Protection measurements 305
Regulations on roentgen ray protection .. 364
Cases of radiation injury 376

Radiobiology

Differentiation and irradiation 57
Protection of living organism against roentgen rays 296

Tumour Biology.

Spontaneous regression of pleural carcinosis 12
Polarographic serum protein reaction 165

Radiophysics

Medical radiophysics in Sweden 191
Periodical inspection of therapy installations 253
Use of radioactive substances in Sweden .. 281
Protection measurements 305
Concentrating roentgen rays for deep therapy 344
Exchange of data between therapy centres 487
Dose measurements on contact therapy tubes 491

Organization

Medical radiophysics in Sweden 191
Periodical inspection of therapy installations 253
Survey of roentgen ray establishments in Sweden 357
Swedish regulations on roentgen ray protection 364
Exchange of data between therapy centres 487
Presentation of results of treatment of cancer 571

Obituary

Rolf Bull Engelstad 485

Editorial

6th International Congress of Radiology, London 1950 ..... 16, 130

List of Authors

Åkerlund, Åke, 147
Anda, Lars, 515
Andersen, S. Ry, 57
Ask-Uppmark, Erik, 104

Benner, Sven, 281
Bichel, Jørgen, 427
Brodén, Bror, 405

Cocchi, Umberto, 115

Eek, Sigurd, 529
Efskind, Leif, 529
Egmark, Agnar, 311
Eklund, Lennart, 376
Engelstad, Rolf Bull, 49

Forssberg, Arne, 165, 206
Frantzell, Arne, 83, 104

Gidlund, Åke S., 421

Heyman, James, 571
Hultberg, Sven, 376

Jennings, W. Alan, 435
Jönsson, Gunnar, 405

Kaae, Sigvard, 539
Kahanpää, V., 412
Karnell, J., 405
Kemp, L. A. W., 17
Kjellberg, Sven Roland, 507
Knutsson, Folke, 557
Köhler, Rolf, 69, 535

Larsson, Lars-Eric, 357, 376
Lindell, B., 344
Lindgren, Erik, 389
Lorentzon, L., 305

Méan, A., 187

Nohrman, Bengt A., 12
Nordlander, Sverker, 165

Olsson, Sten-Erik, 507
Oosterkamp, W. J., 491

Petersen, Olaf, 539
Poppe, Erik, 485

Rennaes, Selmer, 49
Rudhe, Ulf, 147

Sievert, Rolf M., 191, 328, 344

Thoræus, R., 253
Torgersen, Johan, 1, 131

Wahlberg, Thor, 305, 344, 364
van der Werff, J. Th., 31
Wildervanck, L. S., 41
Wolff, Aage, 529

Å, Ä, see A

Ö, Ø, see O